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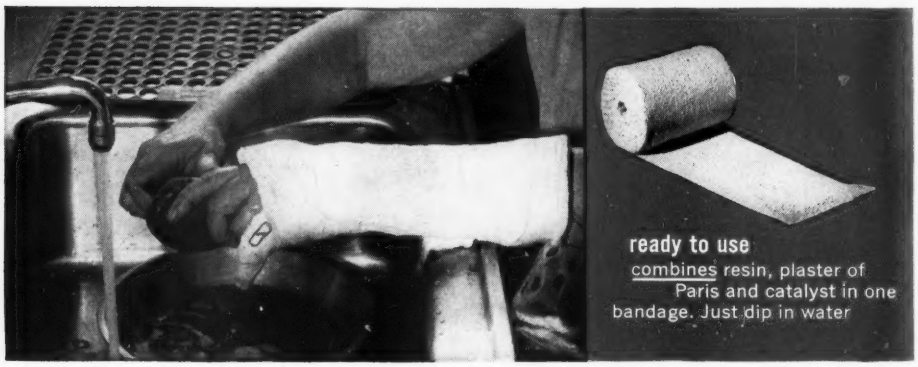

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Annual Subscription: United States and Canada, $15.00; Other Countries, $17.00. Published Monthly. Entered as second-class matter January 14, 1931, at the postoffice at Chicago, Ill., under the Act of Congress, March 3, 1879.

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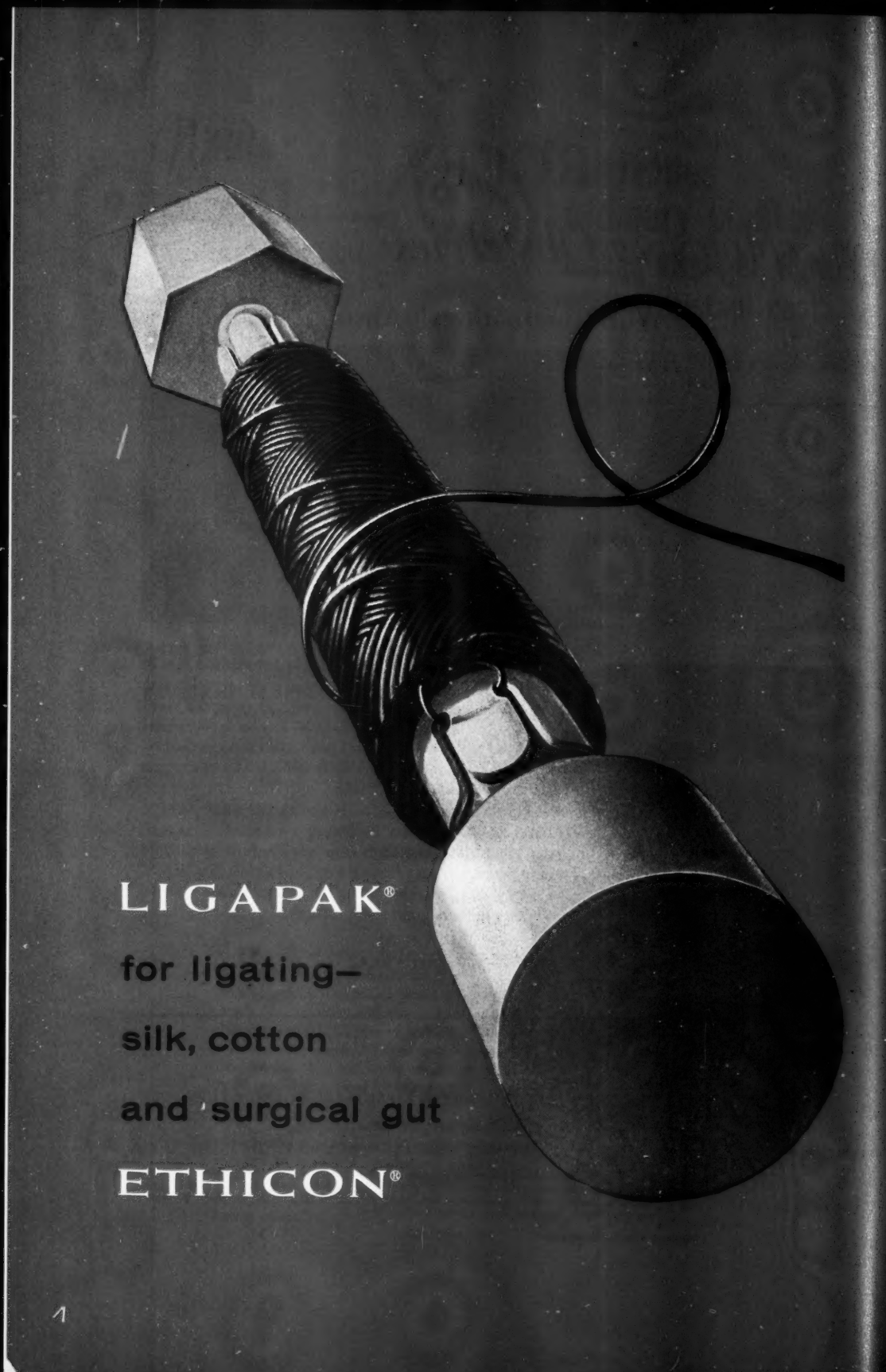
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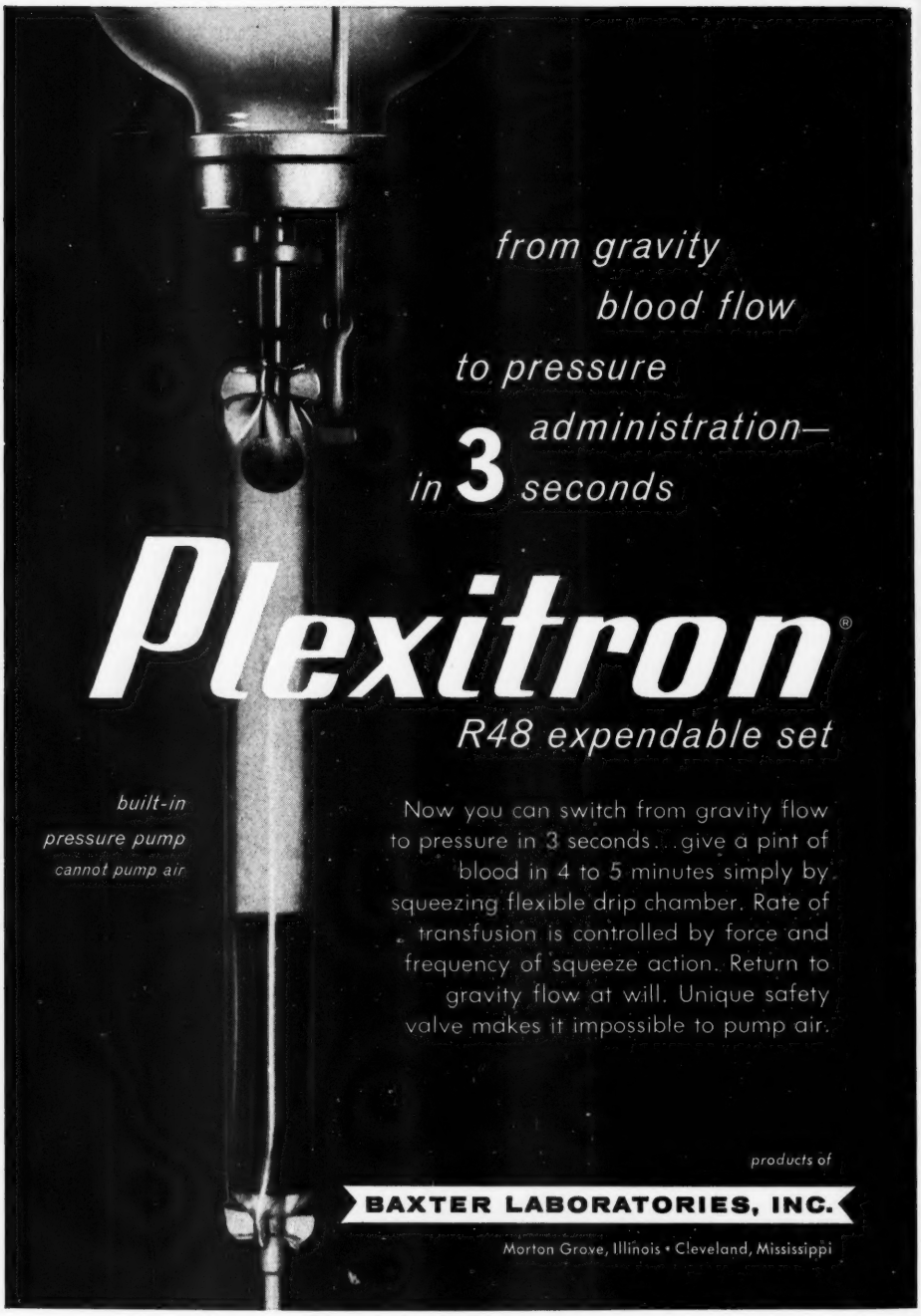
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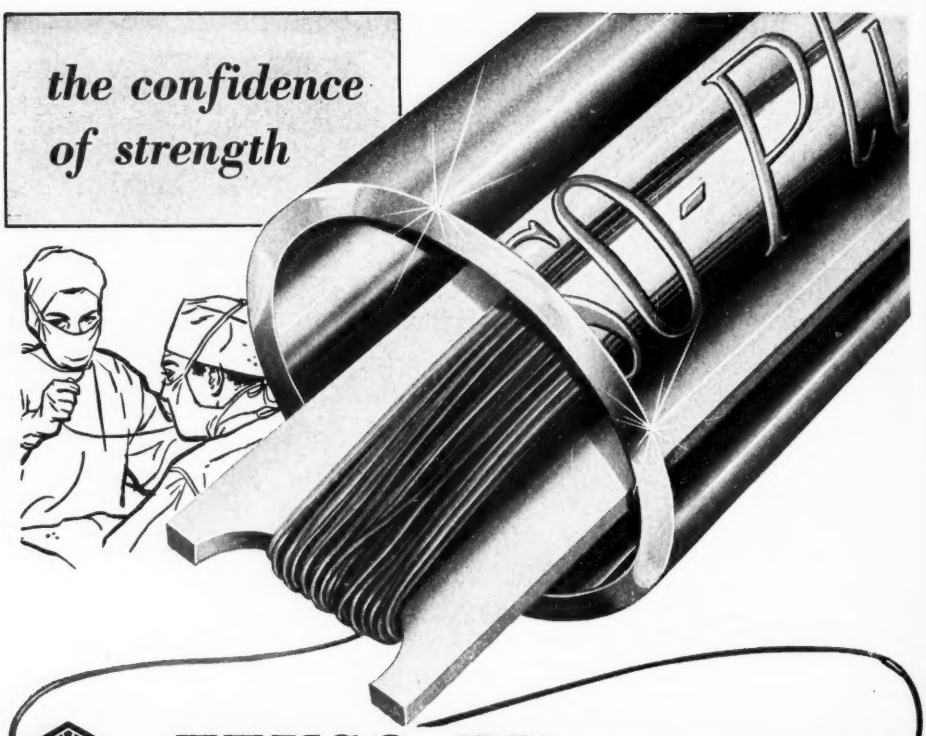

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SURGERY
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POSTOPERATIVE HYPOPARATHYROIDISM

JOSEPH A. BUCKWALTER, M.D., F.A.C.S., ROBERT T. SOPER, M.D.,
JACK DAVIES, M.D., and EDWARD E. MASON, M.D., Iowa City, Iowa

AN EXPLOSIVE ONSET of clinical tetany following operations upon the thyroid gland brings into sharp focus the vital role played by the parathyroid glands in homeostasis. Bell and Bartels reported 58 cases observed following 2,000 thyroid operations performed for thyrotoxicosis, an incidence of just less than 3.0 per cent. Since 1947, at the University of Iowa Hospitals, 18 cases have been noted following 600 operations for thyrotoxicosis, carcinoma, or thyroiditis, an incidence of 3.0 per cent.

Pseudohypoparathyroidism and idiopathic hypoparathyroidism, nonsurgical types of the disorder, occur infrequently and are therefore of less interest to most clinicians. Since 1927, one case of each has been seen at the University of Iowa Hospitals. This report will be concerned with 50 cases of surgically induced hypoparathyroidism seen during this time (Table I). The data have been obtained from the authors' personal experiences incident to the care of recent cases and review of the records of other patients, some of which extend for as long as 28 years. Many of the latter group have been recently examined. We have been especially interested in studying the late effects of the disease as seen in some of these patients in whom the disorder has persisted for many years.

The results of this study have suggested that there is a need for review of relevant embryologic, anatomic, and physiologic considerations and for re-examination of current clinical concepts related to parathyroid deficiency. Review of the pertinent literature suggests that parathyroid dysfunction following surgery is tacitly regarded as usually being transient, and in any case as presenting no particular problem in management, should it prove permanent. Reference is made to complications which may develop with improper management, the implication being that these occur infrequently and are indications of neglect on the part of the responsible physician. Our experience has been to the contrary; permanent parathyroid deficiency following thyroid surgery is not infrequent. Management of these patients is often difficult, and incapacitating complications are not uncommon even in patients under medical surveillance. Failure to note permanent hypoparathyroidism among a large group of patients who have had thyroid surgery

From the Department of Surgery, State University of Iowa College of Medicine, Iowa City, Iowa.

TABLE I.—CLINICAL MATERIAL

	No.
Patients operated upon at University of Iowa Hospitals	37
Operations	
Subtotal thyroidectomy	22
Total thyroidectomy	7
Secondary thyroidectomy	8
Patients operated upon elsewhere	13
Total number of patients studied	50
Diagnoses	
Thyrotoxicosis	36
Non-toxic goiter	6
Carcinoma	7
Thyroiditis	1

Mean age: 39 years. Sex: females 43; males 7.

performed can have two possible explanations: the postoperative follow-up has failed in thoroughness or has not extended for a long enough time.

HISTORICAL REVIEW

The development of our knowledge of the parathyroid glands and their disorders has been recent, gradual, and the result of contributions by many different observers. In 1855 the parathyroid glands were demonstrated by Remak. Virchow published a description of these structures in 1864. It was in 1880 that Sandström described four parathyroid glands, illustrated correctly their relationship to the thyroid gland, and provided their name. He thought that they were probably embryonic thyroid tissue remnants. The first description of tetany as a complication of thyroid surgery was provided by Weiss in the same year. In 1891, Gley showed that the parathyroid glands were functionally separate from the thyroid gland and further, that their preservation prevented tetany from occurring. Loeb demonstrated in 1900 that there was a relationship between the content of calcium in the blood and muscle contraction. During the same year Vassale and Generali noted that ablation of the parathyroids resulted in tetany. The relationship of the parathyroid glands to calcium metabolism was further defined by experiments reported by Erdheim in 1906; parathyroidectomy performed upon rats resulted in faulty calcification of the incisor teeth. The first paper concerned with the surgical anatomy was published by Halstead and Evans in 1907. In 1909, MacCallum and Voegtlin observed that low serum calcium was associated with hypoparathyroidism and suggested a method of treating tetany. Urine phosphorous balance studies were performed by Greenwald in 1911 on parathyroidectomized dogs; he found the urine phosphorous to be decreased. In 1921 Hastings and Murray reported the hydrogen ion concentration and carbon dioxide combining power of the blood to be normal in hypoparathyroid tetany. Vitamin D was shown to be an entity separate from vitamin A and to have an antirachitic effect by McCollum in 1922. In 1922 Salvesen showed depression of the serum calcium accompanying parathyroidectomy to be associated with lowering of the ionized calcium fraction. Hanson in 1923 and Collip in 1925 independently prepared active parathyroid extracts. A crystalline substance was separated from the products of irradiated ergosterol by Askew and associates in 1930 (2, 3); called califerol (vitamin D_2), this is the form of vitamin D most commonly used to treat hypoparathyroidism and rickets. In 1932 the synthesis and use of dihydrotachysterol in treating hypoparathyroidism was described by Holtz. A significant contribution to our understanding of the basic physiologic mechanisms was made by Harrison and Harrison in 1941, when they showed the increased renal excretion of phosphorous caused by parathormone to be related to decreased tubular reabsorption of phosphorous. The years since have seen the clearer definition of the basic physiologic disturbance. At the forefront have been Albright and his co-workers who continue to be engaged in basic investigations of parathyroid function. The accumulation of information by clinicians has in turn better defined the clinical character of the disorder.

EMBRYOLOGY AND ANATOMY

The parathyroid glands develop from two of the five paired endodermal outpocketings of the pharynx which are called pharyngeal pouches. In Figure 1 the various stages in

development are illustrated by diagrams. The pharyngeal area is shown as seen from the right side. In diagram A, depicting the situation at 4 weeks, the anlage of the parathyroids will be noted as proliferations of the epithelium in the dorsal part of the third and fourth pouches; thereafter they are referred to as "parathyroid 3" and "parathyroid 4." Note the common origin of the thymus from the third pouch. With the attenuation of the pharyngeal pouch connections which has occurred by 6 weeks, B, all structures arising therefrom have migrated caudally. Relatively rapid enlargement and descent of the thyroid has occurred; "parathyroid 3" and thymus are still closely associated. By 8 weeks, C, the final adult anatomic relationships are rapidly being assumed. "Parathyroid 3" is now lying near the thoracic inlet caudal to "parathyroid 4." The parathyroid tissue which is frequently located in the root of the neck, within the thymus and in the superior mediastinum, is derived from "parathyroid 3." The final positions and relationships of these structures are shown in diagram D.

The parathyroids are flattened, oval, brownish red bodies lying in juxtaposition to the posterior surfaces of the lateral thyroid lobes (Fig. 2). Their relationship to the thyroid and its false and true capsules, the inferior thyroid arteries, the recurrent laryngeal nerves, and the trachea and esophagus are inconstant. Varying in number from 2 to 6, the individual glands weigh approximately 30 milligrams, measure about 6 millimeters in length and 4 millimeters in width. Variation in their shape and location is well illustrated by a diagram taken from Heinbach (Fig. 3). The fact that they are usually imbedded in adipose tissue, coupled with the aforementioned anatomic considerations, makes identification at the time of surgery difficult and explains the unexpected development of tetany following subtotal thyroidectomy. Interference with blood supply, derived chiefly from the inferior thyroid arteries, is probably the cause of transient hypoparathyroidism. Ligation of

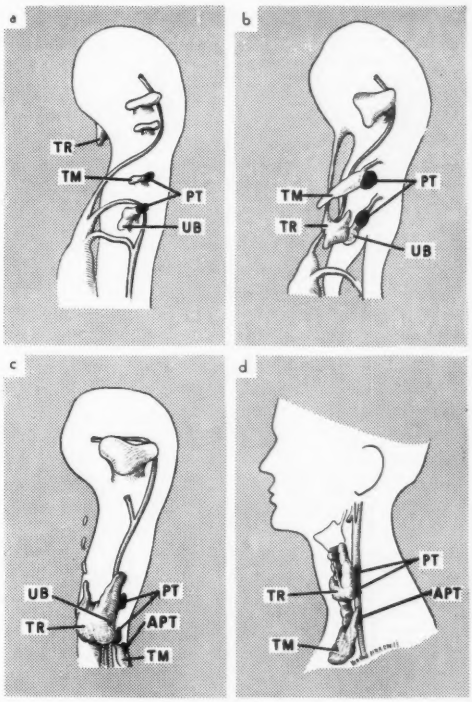
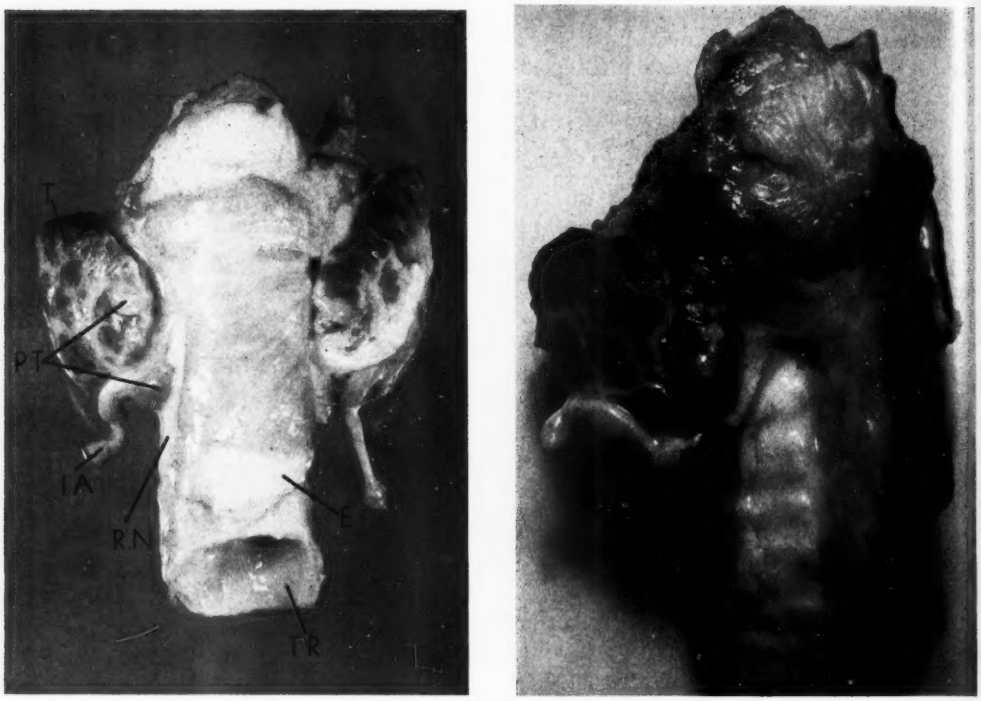


FIG. 1. Diagrammatic representation of the development of the parathyroid glands (*PT*) showing relationships to the thyroid (*TR*), thymus (*TM*), ultimobranchial body (*UB*), and one of the more common positions of aberrant parathyroid tissue (*APT*) at: a, 4 weeks; b, 6 weeks; c, 8 weeks; and d, in the adult. Shown also is the developing carotid artery and aortic arch.

the inferior thyroid arteries away from the thyroid gland might be expected to be an important factor. Bilateral extracapsular ligation of inferior thyroid arteries was done in 19 of the 37 patients operated upon at the University Hospitals. We are unable to determine the significance, if any, of this, since incomplete information on this point is available in the other cases and no data are available which permit comparison with the incidence of hypoparathyroidism when extracapsular inferior thyroid artery ligation is not done. It might be expected that total thyroidectomy as done for cancer would always be accompanied by total parathyroidectomy. This is the exception rather than the rule in our experience and that of Martin. The fact



a b

FIG. 2. a, This fresh postmortem specimen shows the four parathyroid glands (*PT*) viewed from posterior in relation to the esophagus (*E*), thyroid gland (*T*), trachea (*TR*), recurrent laryngeal nerves (*RN*), and inferior thyroid artery (*IA*) on the left. The adipose tissue which enveloped the parathyroid glands has been removed creating an impression of accessability which is never true at time of surgery. b, Specimen viewed from left side.

that one or more of the parathyroid glands are frequently located deep in the tracheal esophageal groove, not in juxtaposition to the thyroid gland or its true capsule, is the most likely explanation.

The microscopic anatomy is characterized by groups and cords of epithelial cells and a network of sinusoidal capillaries with a framework of reticular fibers. Present evidence suggests that the predominant chief cell is associated with the elaboration of parathormone. Oxyphil cells become more numerous with advancing age; their functional significance is not understood (Fig. 4).

PHYSIOLOGY

The basic physiology of the parathyroid glands is shown diagrammatically in Figure 5. Lowering of ionized serum calcium is the stimulus responsible for the release of parathormone. Currently it is believed that the main action of the latter is upon the kidney. Decreased tubular reabsorption of phosphorous results in increased excretion of this anion. Of lesser magnitude is the effect which parathormone exercises to increase the absorption of calcium from the gastrointestinal tract. In contrast, the effect of vitamin D_2 is almost limited to promoting calcium absorption. There is both clinical and experimental evidence to suggest that parathormone increases osteoclastic activity which is well demonstrated by decalcification occurring in the patient with a parathyroid adenoma resulting in osteitis fibrosa cystica. The net result of these three parathormone effects is a dynamic equilibrium with serum calcium and phosphorous levels,

maintained within narrow limits. Removal or damage to the parathyroids upsets this equilibrium with a rapid increase in serum phosphorous, lowering of the serum calcium, and prompt development of the clinical syndrome tetany.

All workers active in this field of investigation are not in agreement with this interpretation of parathyroid physiology. Since it is not the purpose of this article to delve into this controversial matter, the concept has been presented which seems to be most widely accepted and best supported by the available clinical and experimental data.

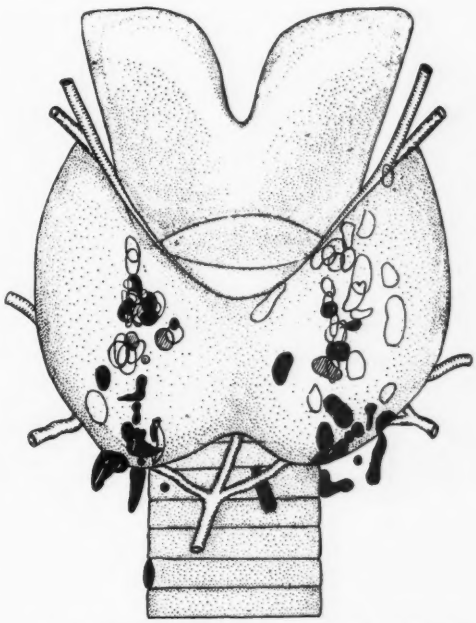


FIG. 3. Diagrammatic representation of variation in size, shape, number, and position of parathyroid glands observed at the time of 25 cadaver dissections. (From Heinbach, W. F., Jr. *Anat. Rec.*, 1933, 56: 251–261.)

DIAGNOSIS

The remainder of this report will deal with the clinical problem as seen in our group of patients (Fig. 6). Onset of clinical hypoparathyroidism occurred most often during the week following operation. Tingling, paresthesias, and numbness of the fingers and toes were the most common presenting symptoms. Tonic spasms of the fingers and toes (carpopedal spasm) and evidence of increased neuromuscular irritability (Trousseau's, Chvostek's, and Erb's signs) were present at this time, or soon appeared. Tightness and stiffness of other muscle groups, a feeling of restriction of freedom of inspiration and expiration, hyperventilation, and laryngospasm occurred much less frequently and later. The numbers of these patients experiencing the various symptoms and physical signs are listed in Table II.

In a patient who has recently undergone thyroid surgery, the appearance of these symptoms and signs is pathognomonic of parathyroid insufficiency. Laboratory determinations done at the onset showed depression of the serum calcium, elevation of the serum phosphorous, and decreased or absent calcium in the urine as determined by the Sulkowitch test. Further confirmation of the diagnosis is provided by the prompt disappearance of the symptoms when calcium is administered intravenously.

Differentiation from tetany caused by other disorders, that is, tetany of the newborn, osteomalacia, infantile rickets, chronic steatorrhea, pregnancy, renal failure when acidosis is corrected, loss of gastric juice, sodium bicarbonate therapy, or hyperventilation—or from nonsurgical hypoparathyroidism (Table III) is rarely difficult because of the clear cut history. Occasionally a problem is presented in differential diagnosis by the development of the symptoms and signs of tetany unassociated with recent thyroid surgery. Of more importance is the recognition of hypoparathyroidism, surgical or nonsurgical, as the cause of cataracts, convulsive episodes, mental deterioration, and psychosis. Patients with these late sequelae may have none of the typical symptoms or signs which have been discussed.

TREATMENT

Infrequently the onset of the hypoparathyroid state will be announced by the rapid

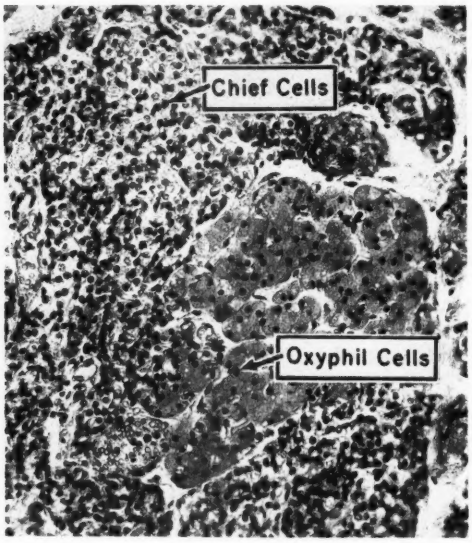


FIG. 4. Photomicrograph of parathyroid gland. × 85.

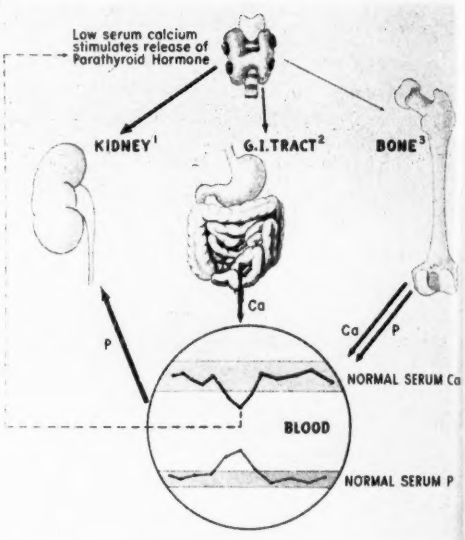


FIG. 5. Basic physiology of the parathyroid glands.

development of frightening respiratory difficulty resulting in frantic efforts by the patient to increase pulmonary ventilation, leading to rapid, shallow respirations and aggravation of all symptoms. Intravenous calcium administration (calcium chloride or gluconate 10 ml. of a 10 per cent solution) results in prompt correction of the hyperpneic state and improvement of the more common tingling, muscle cramps, paresthesias, numbness, and signs of increased neuromuscular irritability. This improvement results from the interruption of a vicious cycle. By raising the ionized serum calcium level, psychic and organic factors leading to neuromuscular excitability and spasm are corrected, resulting in slower and deeper respirations, leading to correction of the respiratory alkalosis. In the unusually severe case it may be necessary to repeat this dose one or more times until satisfactory control has been obtained with definitive therapy.

TABLE II.—SYMPTOMS AND SIGNS OBSERVED

	No. of patients
Chvostek's sign	33
Tingling	30
Muscle cramps	29
Carpal spasm	23
Trousseau's sign	21
Pedal spasm	20
Numbness	14
Paresthesias	9
Stiffness	8
Disorientation	6
Twitching	6
Convulsions	5
Ringing in ears	4
Hyperventilation	3
Erb's sign	3
Laryngospasm	2
Dysphagia	2
Anxiousness	2

Parathormone may be useful, although it is rarely necessary during this early period. Its continued use results in a refractory state within a matter of a few weeks or months so that even large doses will have no effect. This fact combined with its relatively high cost makes parathormone of little practical importance in the management of this disorder.

Vitamin D_2 (50,000 to 200,000 units daily) and oral calcium (calcium lactate powder 5 to 15 grams daily) should be started as soon as the diagnosis is made. Various preparations of both these medications are available which are equally effective. The correct dosages are determined by following the patient's course, serum calcium, and phos-

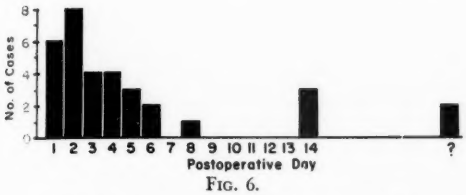


FIG. 6.

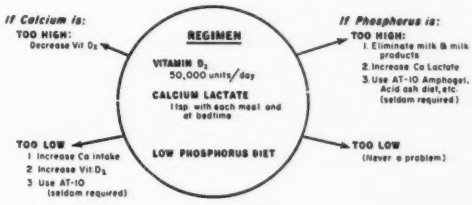


FIG. 7.

IG. 6. Day of onset of symptoms and signs of tetany.
IG. 7. Use of serum calcium and phosphorous levels in management of surgical hypoparathyroidism.

phorous levels (Fig. 7). After control of the parathyroid deficiency has been achieved, serum determinations will be required only infrequently but must be continued throughout the patient's life if the disorder proves permanent. The urine Sulkowitch test can be effectively used by the patient in long term management somewhat as urine sugar determinations are used by the diabetic patient in the management of his disease. In addition to vitamin D_2 and calcium, it is most important to place the patient on a low phosphorous diet. Intake of meat, fish, whole grain cereals, and dairy products, all relatively high in phosphorous, should be limited to basic requirements.

Vitamin D_2 toxicity is related to abnormally high ionized serum calcium levels. The possibility of toxicity must always be remembered since there is considerable variation in the size of the therapeutic and toxic doses in different patients. Nausea and vomiting, the most common early symptoms, should cause one to reduce the dose. Ectopic calcification occurs only when excessive doses have been administered for a prolonged time. By comparison, calcium is not toxic. It is therefore prudent first to increase the amount of calcium being administered to an incompletely controlled patient if therapeutic doses of vitamin D_2 are being given. This is especially true in the patient with an unusually high serum phosphorous level. In addition to making available increased amounts of calcium for absorption from the gastrointestinal tract, the formation of calcium phosphate salts is promoted, thereby decreasing the amount of phosphorous available for absorption. Whenever the serum phosphorous is very high, it is important to make certain first that a low phosphorous diet is being followed, secondly, that there is no renal failure.

Because of its relatively high cost, dihydrotachysterol (A.T. 10) should be reserved for the exceptional case which cannot be managed with vitamin D_2, calcium, and diet. The effect of dihydrotachysterol is about midway between parathormone and vitamin D_2, that is, while having more effect on the kidney than vitamin D_2, it has less than parathormone, more effect on calcium absorption than parathormone, but less than vitamin D_2. Before a decision is made that dihydrotachysterol is required, an adequately supervised trial with vitamin D_2, calcium, and low phosphorous diet should be extended a week or more employing the maximum indicated doses.

Pertinent information regarding the medications used in the management of this disorder is summarized in Table IV. After satisfactory control has been achieved as indicated by the absence of signs and symptoms and normal serum calcium and phos-

TABLE III.—DIFFERENTIAL DIAGNOSIS OF TETANY

	Hypoparathyroidism			*Nonparathyroid tetany*
	Post-operative	*Idiopathic*	*Pseudo*	
Signs and symptoms of tetany	+	+	+	+
Serum Ca ↓ P ↑ Urine Ca ↓ P ↓	+	+	+	±
Thyroid surgery	+	−	−	−
Response to parathormone	+	+	−	−
Extraparathyroid tetany factor	−	−	−	+

TABLE IV.—MEDICATIONS USED IN TREATMENT OF HYPOPARATHYROIDISM

Medication	*Composition and dose*	*Route*	*Action, advantages*	*Expense, cost per day*
Parathyroid hormone	50 u. = 1 ml. Dose: 1 ml. per day	I.M.	May be used for initial treatment. Expensive, unnecessary, and ultimately ineffective. Used primarily as a test (Elsworth-Howard) to differentiate hypoparathyroid-like states from true parathyroid deficiency	$0.70
AT-10, Dihydrotachysterol	2 capsules = 1 ml. liquid form; 1 ml. = 1.25 mg.n. pure A.T. 10 Dose: 2-8 caps. per day	Oral	Simulates the action of parathyroid hormone more closely than Vitamin D_2 but not sufficiently to justify its use because of its expense. Needs to be supplemented with ↑ Ca ↓ P intake	$0.55–$2.20
Vitamin D_2	50,000 u. caps. Dose: 1–4 caps. per day	Oral	Cheap and effective when used in conjunction with ↑ Ca ↓ P intake	$0.03–$0.12
Calcium lactate powder—high calcium intake	1 tsp. = 3 gms. Dose: 1 tsp. t.i.d. and h.s. in drinks other than milk	Oral	High calcium ingestion not only supplies Ca for absorption but ties up P as insoluble $Ca_3(PO_4)_2$ which is lost in the stool, thus keeping serum P ↓	$0.008
Low phosphorus intake	High phosphorus content makes milk undesirable	—	This is one of the easiest and yet most often neglected adjuncts. Milk has been prescribed erroneously in the belief that its high calcium content would make it desirable	—
Calcium gluconate, 10%	Dose: 10 ml. sterile ampule	I.V.	Used only in treating acute attacks of severe tetany. Seldom required	—

phorous values, the primary responsibility for management must be shifted to the patient. He must be carefully oriented regarding the nature of his problem and painstakingly instructed in its management. Proper regulation is obtained by taking sufficient medication so that no signs or symptoms of tetany are present. The use of the Sulkowitch test provides real assistance to the patient. (Fig. 8). Satisfactory control exists if an early morning urine specimen shows a + precipitate. If none is present, the serum calcium is low and the dosages of medications should be increased; a +++ precipitate indicates overtreatment and dosages should be decreased. One of the greatest values of the Sulkowitch test is in preventing overtreatment. In order to assure adequate management it is necessary to obtain periodic serum calcium and phosphorous levels for as long as the disorder persists. Of importance is periodic re-evaluation by an informed physician. The patient with permanent hypoparathyroidism is to be regarded as having a lifelong metabolic disease in every sense as serious as diabetes mellitus and requiring equally assiduous attention to the details of management.

TABLE V.—LATE COMPLICATIONS

	No. of patients
Cataract	10
Convulsions	7
Mental deterioration	3
Psychosis	2
Cardiac insufficiency	1
Death	1

COURSE

The early clinical course of this disorder does not appear to differ whether the deficiency ultimately proves to be transient or permanent. Time and character of onset, symptoms and signs, biochemical disturbances, and the response to treatment remain similar in the two groups of cases for as long as the deficiency persists. Since it is impossible to predict the course of the disorder on the basis of clinical or laboratory findings, periodic discontinuance of treatment is therefore necessary to determine whether the disorder persists and whether further treatment is

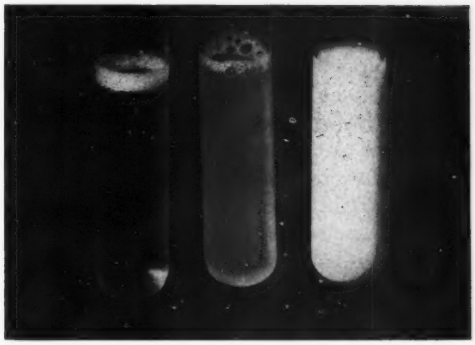
necessary. One year was arbitrarily chosen as the time dividing the two groups. There were no patients in whom the disorder had persisted for a year or more who reverted to normal.

Sufficient data were available regarding 33 patients to permit their classification as transient or permanent hypoparathyroidism: 25 were permanent and 8 transient. Of the 13 patients in whom surgery was performed elsewhere than the University Hospitals, all had permanent hypoparathyroidism. Because of incomplete data or too short a time since surgery, classification of the remaining cases was not possible.

It should be emphasized that late in the course of the disorder, absence of symptoms and signs when treatment is discontinued does not necessarily mean that the patient has normal parathyroid function. The only indication of the persisting deficiency may be marked depression of the serum calcium and elevation of the serum phosphorous. Final tragic confirmation is too often provided by development of serious late complications in those patients in whom appropriate measures are not taken to correct the persisting defect in calcium phosphorous metabolism.

In Table V are listed the late complications seen in this group of patients. Cataracts were noted as soon as 1 year following operation in a patient with uncontrolled hypoparathyroidism. Several of the 7 patients developing cataracts who were operated upon elsewhere than at the University Hospitals were referred for treatment without recognition of the hypoparathyroid state. Similarly, hypoparathyroidism was not recognized in another patient as the probable cause of a convulsive disorder and mental deterioration. This patient died at the age of 38 years with myocardial fibrosis in the presence of normal appearing coronary arteries.

Time and character of onset, the early clinical pattern relative to the nature and severity of symptoms and signs, and response to treatment could not be related to the development of these late sequelae any more than to the transient or permanent nature of the disorder.



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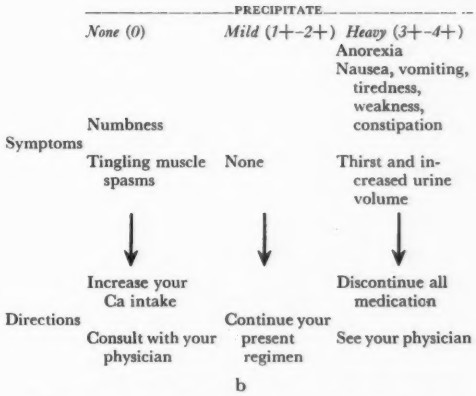

b

FIG. 8. a, The Sulkowitch urine test. b, Instructions to the patient regarding use of the test and management of the disorder.

The only apparent common denominator was a prolonged period during which the hypoparathyroid state was permitted to remain uncontrolled. As has already been stated, during this period there were frequently none of the "typical" symptoms and signs of the disorder. It is imperative that treatment be continued until serum calcium and phosphorous levels remain normal and clinical remission persists during a prolonged trial without therapy. Unless the necessary vigilance is exercised to enforce this dictum, inevitably the unfortunate patients will suffer the consequences.

SUMMARY

A series of 50 patients with surgically induced hypoparathyroidism has been presented. The basic background material relative to this disorder has been reviewed. Symptoms and signs noted were reported; clinical considerations of diagnosis, treatment, and the course of the disorder have been discussed. It is suggested that perhaps the full importance of a continuing long term follow-up of these patients has not been generally recognized. Attention is called to the fact that progression to late irreversible sequelae, which include cataract, convulsive disorders, and mental deterioration, can occur in a patient who has continuing uncontrolled hypoparathyroidism although having none of the common clinical stigmas of the disorder. Alertness in diagnosis and enlightened management with constant and continued vigilance are required if these late sequelae are to be avoided. The patient must be informed of the dangers of poor control and the means whereby these dangers may be circumvented. Hypoparathyroidism is a clinical problem deserving of more attention by the medical profession.

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TOTAL EXCISION OF THE AORTIC ARCH FOR ANEURYSM

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AT THE PRESENT TIME the treatment of choice for aneurysms of the aorta is excision with preservation or restoration of aortic continuity. Certain factors, however, such as the location and nature of the lesion, may limit the successful application of this method of surgical therapy in thoracic aneurysms. In sacciform lesions, for example, as was indicated in our original report on this problem (1), resection is possible in virtually all cases, since this may be done by tangential excision and lateral aortorrhaphy without interruption of aortic flow. In fusiform aneurysms, on the other hand, which involve the entire circumference of the aorta, temporary occlusion of the aorta above and below the lesion is necessary in order to permit excision of the diseased segment and restoration of circulatory continuity by means of an aortic homograft or synthetic prosthesis (2). During the period of arrest of aortic circulation, serious ischemic damage may occur to tissues located distally, depending upon the duration and level of occlusion. Obviously, the more proximal the lesion and the higher the point of occlusion the greater is the likelihood of ischemic damage to vital organs and especially to the spinal cord which is highly vulnerable to such anoxic effects. Accordingly, this factor assumes particular importance in the resection of aneurysms located about the aortic arch. Our clinical and experimental observations (3, 7) have shown that it is possible to overcome this factor with the use of hypothermia. This therapy has been found to be an effective means of prolonging the safe period for temporary arrest of aortic circulation as high as the level of the left subclavian artery for a sufficient time, about 1 hour, for the performance of the procedure. With the aid of this measure virtually all aneurysms of the thoracic aorta located distal to the origin of the left common carotid artery may be considered resectable.

For fusiform aneurysms arising at a higher level the problem of resection becomes much more difficult and hazardous. Under these circumstances the necessity to clamp the ascending aorta proximal to the origin of the carotid arteries imposes serious cardiac effects in addition to the dangers of ischemic damage to the brain and spinal cord. For this reason excisional therapy of aneurysms located at this level has been limited almost entirely to tangential resection of sacciform lesions, which may be done without interruption of aortic circulation. Significantly the only cases of total resection of the aortic arch, reported by Schafer and Hardin and by Stranahan and associates, resulted in death of the patients in the operating room. Recently we had a case in which total arch resection was accomplished under hypothermia using temporary by-pass shunts in which the patient survived 6 days, and the purpose of this article is to consider briefly some of the technical aspects of the surgical problem.

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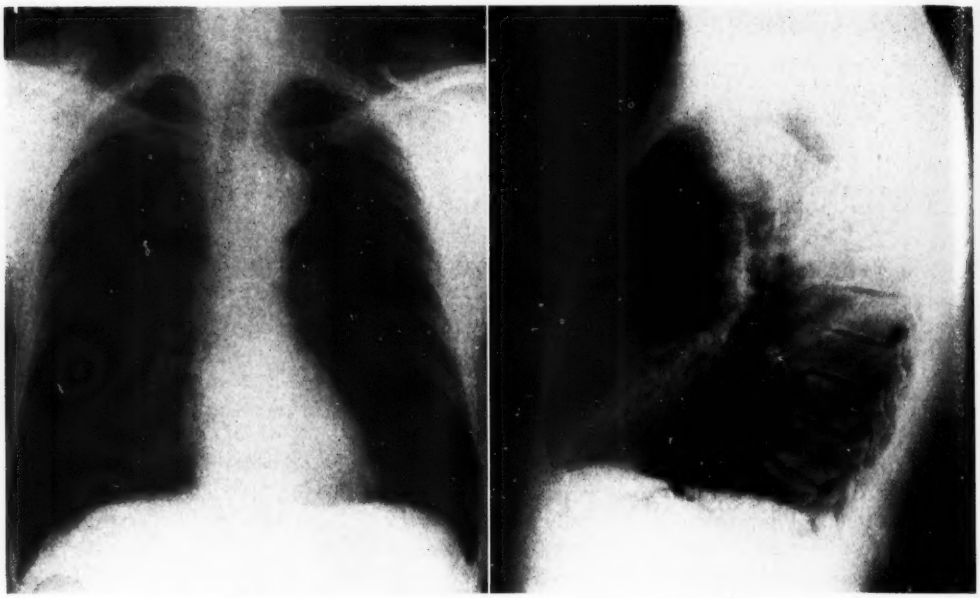
Supported in part by a grant from the Houston Heart Association, and the Cora and Webb Mading Fund for Surgical Research.

CASE REPORT

E. L., a 49 year old white male, was admitted to Methodist Hospital on June 20, 1955, with pain in the left side of the precordium for 6 months and a nonproductive cough. The patient had contracted primary syphilis approximately 30 years previously but had had no specific treatment until 1939, at which time he received multiple injections of bismuth and arsenicals. Recently, because of the onset of the presenting



a b

FIG. 1. Roentgenograms of the chest showing a partially calcified fusiform aneurysm involving the entire aortic arch and a smaller aneurysm in the proximal portion of the descending thoracic aorta. a, Posteroanterior view; b, lateral view.

symptoms he received an intensive course of penicillin therapy without relief of symptoms.

Physical examination revealed increased retromanubrial dullness to percussion but there were no abnormal precordial pulsations. Blood pressure was 120/80 millimeters of mercury and the pulse was regular. The heart sounds were normal and there were no murmurs.

Routine laboratory studies were within normal limits and serologic test for syphilis was negative. Roentgenograms of the chest revealed a partially calcified fusiform aneurysm involving the entire aortic arch with a second smaller aneurysm originating just distal to the great vessels in the descending aorta (Fig. 1). The electrocardiogram revealed no abnormality.

At operation on June 24, 1955, general anesthesia was induced with intravenous pentothal® and the patient's rectal temperature was reduced to 93 degrees F. by surface cooling, using ice water and dilute alcohol supplemented with a single intravenous injection of 25 milligrams of chlorpromazine. With the patient in the supine and partly lateral position a left anterior thoracotomy was performed through the third intercostal space. After preliminary exploration of the chest had confirmed the presence of an aneurysm, the incision was extended across the sternum into the right third intercostal space, but the right pleural space was not entered. A vertical median sternotomy incision was then made extending into the suprasternal notch, providing adequate exposure of the aortic arch and major branches. The fibrofatty tissue in the anterior mediastinum was dissected away from the major vessels, and the pericardium overlying the ascending aorta was opened transversely. Because of the second aneurysm in the proximal portion of the descending aorta and the need for exposure of the lower portion of this segment of aorta, an intercostal incision was made in the left sixth space using the original skin incision and detaching the serratus anterior muscle from the underlying ribs. The ascending and descending thoracic aorta and the three major branches from the aortic arch were mobilized and encircled with tapes for traction.

The shunts which were made of compressed polyvinyl sponge (ivalon®) were sutured into place end-to-side using partial tangential occlusion clamps on the aorta and carotid arteries for this purpose (Fig. 2). When the ascending aorta was cross-clamped, the bypass which had an internal diameter of 14 millimeters carried the entire cardiac outflow and systolic blood pressure recorded in the legs fell only 10 millimeters of mercury from 90 to 80 millimeters of mercury. Shortly after clamping the ascending aorta the heart rhythm became irregular due to frequent extrasystoles and continued for a period of several minutes

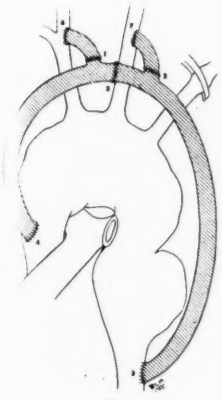
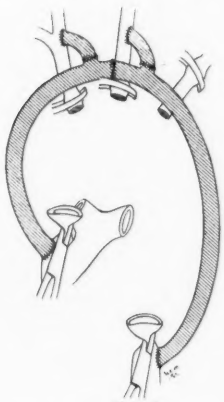


FIG. 2.



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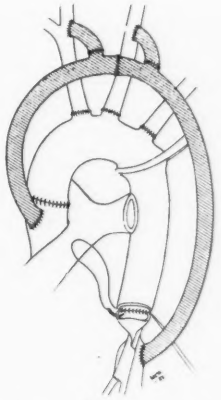

FIG. 4.

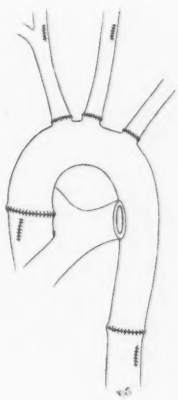

FIG. 5.

FIG. 2. Drawing showing the technique of utilization of by-pass shunts to conduct blood from the ascending to the descending aorta and also into the innominate and left common carotid arteries during total arch excision and insertion of ivalon prosthesis.

FIG. 3. Drawing showing the functioning by-pass after excision of the entire aortic arch and proximal portion of descending thoracic aorta.

FIG. 4. Drawing showing anastomoses completed between the ascending aorta, innominate, left common carotid and left subclavian arteries and the compressed ivalon prosthesis permitting blood to circulate through these branches while the terminal anastomosis is performed.

FIG. 5. Drawing showing ivalon prosthesis in place after removal of the temporary by-pass.

after which regular sinus rhythm returned spontaneously. The left subclavian artery was occluded temporarily by a bulldog clamp. During this time the shunt provided circulation to the right subclavian and both carotid arteries, and strong pulsations were palpable in these vessels. The entire arch, as well as a portion of the descending aorta, was excised preserving the vagus and recurrent laryngeal and phrenic nerves (Fig. 3). The innominate, left carotid, and the left subclavian anastomoses were performed in that order using No. 0000 arterial silk. While completing the subclavian anastomosis the anesthetist reported that he was unable to feel a right carotid pulse. The proximal anastomosis to the ascending aorta was rapidly completed and the clamp was removed after 54 minutes of aortic occlusion (Fig. 4). Thus, blood was permitted to flow through the proximal portion of the prothesis and carotid pulses returned bilaterally. The right carotid pulse was absent for approximately 8 minutes. The distal aortic anastomosis was completed 21 minutes later and the aortic clamps were removed. The prosthesis functioned quite satisfactorily, and there was minimal blood loss after removal of the clamps. The shunt was then removed and the openings in the various vessels were oversewn with arterial silk sutures (Fig. 5). The dimensions of the prosthesis appeared to be ideal and there was no kinking or disproportion noted (Fig. 6). The incisions in the chest wall were then closed with chromic catgut and silk sutures, and catheters were placed into the left pleural space for underwater drainage. At the completion of the operation which lasted 8 hours, the patient's condition was stable and rectal temperature was 91 degrees F.

Rewarming was accomplished in a hydrotherapy tank at a water temperature of 112 degrees F., and the patient was removed from the tank 45 minutes later when his rectal temperature had risen to 99 degrees F. Respirations were normal and blood pressure was 120/80 millimeters of mercury. Pulses were palpable in all extremities and in the carotid arteries.

Although his general condition otherwise was very satisfactory, he did not regain consciousness. Twenty-four hours later he responded to painful stimuli and ophthalmic reflexes were normal. During the ensuing 5 days the lungs remained expanded and the prosthesis functioned well. Pulses were easily palpable and his blood pressure ranged around 130/80 millimeters of mercury. Although from time to time his state of consciousness seemed to improve somewhat, his condition began to deteriorate, and he died on the sixth day after operation.

Autopsy revealed that the prosthesis was intact and contained no thrombi. The brain showed no evidence of ischemic necrosis.

DISCUSSION

In general, the two major obstacles to successful resection of the entire aortic arch are

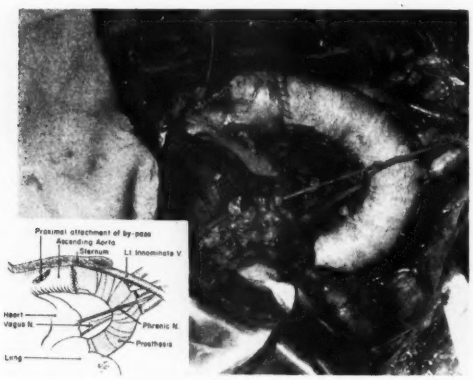

FIG. 6.

FIG. 7.

FIG. 6. Photograph made at thoracotomy showing ivalon prosthesis in place and the anastomoses to the ascending aorta and vessels of the arch. The drawing in the inset indicates the origin of the anastomoses to the great vessels of the arch and identifies other structures.

FIG. 7. Photograph showing the glass forms which were used to make the by-pass shunts as well as the prosthesis, and a compressed polyvinyl sponge prosthesis which has been removed from the form.

acute cardiac failure from ventricular strain and ischemic damage to the brain and spinal cord during temporary occlusion of the ascending aorta. Two methods of dealing with these problems are available, namely, the use of by-pass shunts to conduct blood around the diseased segment during its excision and replacement, and the use of hypothermia to reduce cardiac output and oxygen demand by the tissues.

Cross clamping the ascending aorta in animals leads to cardiac failure from left ventricular strain after relatively few heart beats. Izant, Hubay, and Holden have shown experimentally in dogs that a by-pass shunt measuring only 5 millimeters in diameter will preserve 80 per cent of the systemic blood flow and adequate pressure distal to the proximal occluding clamp to prevent ischemic damage to the spinal cord. Undoubtedly, the use of larger shunts would provide a more satisfactory flow distally and at the same time control hypertension in the segment of aorta between the left ventricle and the proximal clamp. For this reason, in our case, a relatively large shunt with an inside diameter of 14 millimeters was used and it is noteworthy that systolic blood pressure in the legs fell only 10 millimeters of mercury when the shunt was open and the ascending aorta was occluded. Hypertension in the proximal segment was probably minimized not only by the large caliber shunt but also by the hypothermic state which reduced cardiac output. Shortly after applying the clamp numerous extrasystoles were noted for several minutes but these disappeared and cardiac action remained stable for the remainder of the interval during insertion of the prosthesis.

With the exception of the central nervous system all organs lying distal to an occluding aortic clamp will tolerate periods of circulatory interruption for the average period of time, approximately 1 hour, required to accomplish the technical steps in aortic aneurysmectomy. Because of our previous experience (2, 3, 7) with hypothermia as an adjunct to surgical treatment of thoracic aneurysms, both hypothermia and by-pass shunts were employed to increase the margin of safety in the prevention of cardiac and neurologic damage.

Instead of using an aortic homograft in this case as has been our custom in segmental replacements of other regions of the

thoracic aorta, a compressed polyvinyl sponge (ivalon) prosthesis was employed because it provided a larger lumen tube to accommodate the somewhat dilated proximal and distal lumens of the aorta and also because the origins of the great vessels branching off the arch could be spaced sufficiently far apart to provide access for individual suturing. Accordingly, the prosthesis as well as the shunts were made of polyvinyl sponge, the use of which was first investigated in experimental animals by Grindlay and Waugh, in 1951. The glass forms which were used in producing the ivalon tubes were made by a professional glass blower using the measured 21 millimeter diameter of the aorta in the roentgenogram as a guide for making the arch prosthesis and the arbitrary 14 millimeter diameter for the shunt (Fig. 7). A method described by Mortenson was followed in which strips of wet ivalon were wrapped in layers on the glass tubes and compressed by an outer tight wrapping of ordinary gauze bandage. The glass forms and prostheses were autoclaved at 220 degrees F. for 20 minutes in a pan of distilled water following which the gauze wrapping and compressed sponge were removed from the forms. Such grafts are porous yet have a remarkably smooth inner lining. Moreover, the texture of these elastic tubes is favorable for suture, and bleeding around needle holes does not occur. On the basis of encouraging results of experimental use of such prostheses by Mortenson and by Shumway, Gliedman, and Lewis and of our own clinical experiences with 6 other cases of aortic grafts, this material can be recommended as a favorable arterial substitute for vessels of large caliber.

Death of the patient 6 days after operation was due to cerebral damage from temporary ischemia resulting from thrombosis of the right carotid shunt which occurred during the insertion of the ivalon prosthesis. Approximately 8 minutes elapsed from the time the thrombosis in the shunt was recognized until the clamp on the ascending aorta was released and carotid flow was re-established. Perhaps such technical complications of the procedure could be avoided by use of heparin either locally or systemically or preferably by siliconizing the inside of the tubes. Except for the accident which subsequently led to death of the patient the operation was performed without great difficulty. The fact that the patient survived the operation and lived for 6 days, during which time all peripheral pulses were readily palpable, testifies to the feasibility of total arch resection from a technical standpoint and justifies further attempts of this kind. Utilization of hypothermia in this case probably controlled the extent of cerebral injury which occurred preventing an earlier fatality and on this basis may be recommended as a useful adjunct to therapy in such cases.

SUMMARY

Excisional therapy for aneurysms of the aorta is now established as the method of choice. For fusiform aneurysms this procedure involves cross clamping the aorta above and below the diseased segment following which the lesion is excised and circulatory continuity is restored by means of an aortic homograft or prothesis. Temporary arrest of aortic circulation thus becomes the major hazard in the successful application of this procedure. This is particularly true for lesions lying in the aortic arch and requiring temporary occlusion of the ascending aorta. The two major obstacles under these circumstances are ischemic damage to the brain and spinal cord and cardiac failure from left ventricular strain. To overcome these problems two measures may be employed, namely, hypothermia and by-pass shunts.

A case is reported in which total excision of the aortic arch was performed followed by replacement with a prosthesis made of compressed polyvinyl sponge (ivalon). The patient survived 6 days during which period the prosthesis functioned well. The combined use of hypothermia and by-pass shunts in this particular case is considered to have contributed materially to the feasibility of the procedure.

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THE CLINICAL VALUE OF COLONIC EXFOLIATIVE CYTOLOGY IN THE DIAGNOSIS OF CANCER BEYOND THE REACH OF THE PROCTOSCOPE

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THE DIAGNOSIS OF COLONIC CANCER may be suspected clinically, but, as a rule, the diagnosis is established by the roentgenologist and proctoscopist. Not infrequently, however, the x-ray evidence is insufficient clearly to differentiate a benign from a malignant lesion; occasionally an early carcinoma may be completely overlooked.

In the recent literature there is no general agreement concerning the usefulness of colonic exfoliative cytology in detecting malignant lesions of the large bowel beyond the reach of the proctoscope. Wisseman and associates found definite tumor cells in 5 of 19 cases of proved carcinoma in or proximal to the sigmoid. Blank and Steinberg recovered malignant cells in 1 of 19 cancers when the smears were taken from a discharge below the lesion. In both series the exudate and mucus were collected during proctoscopy by a cotton swab.

Bader and Papanicolaou performed colonic washings in 19 patients in whom a lesion was suspected beyond the reach of the proctoscope. They correctly diagnosed a cecal carcinoma by this method for the first time. Rubin and associates performed colonic washings in 55 patients and correctly diagnosed 27 of 33 colonic cancers; 2 of the tumors involved the cecum and 1 was located in the hepatic flexure. These results indicated that malignant cells could be recovered from the right colon.

This study was facilitated by grants from the Illinois Branch of the American Cancer Society and the Stewart Fund to The University of Chicago.

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The purpose of this report is to describe our experience with colonic exfoliative cytology during an 18 month period, as an aid in the diagnosis of colonic lesions beyond the reach of the proctoscope; two different techniques have been evaluated and compared.

MATERIALS AND METHODS

A colonic lesion was suspected clinically in each case. Patients with lesions visualized at proctoscopy and accessible to adequate biopsy were excluded from the study. Patients with chronic ulcerative colitis were excluded from this report and are reviewed in a separate communication (3).

During a period of 18 months, colonic washings were performed on 68 patients; follow-up information is available on 59. Pathologic confirmation of malignancy became available in 26 cases. In 32 patients colonic cancer subsequently was excluded, by surgery in 14 patients and by clinical observation in 18 cases. Of the latter, 10 patients were personally contacted by mail; in none was any information elicited suggestive of colonic cancer, 8 to 15 months after examination. The clinical follow-up periods in the 18 cases were 4 months in 2, 6 to 7 months in 2, 8 months in 3, 10 to 11 months in 5, 13 to 15 months in 3, and 16 to 18 months in 3. One patient thus far has refused surgery. In 9 patients no follow-up information is available.

The colon was prepared by the administration of 2 ounces of castor oil 24 hours prior to the examination and by the use of tap water enemas the night before and on the morning of the test. The patients were given

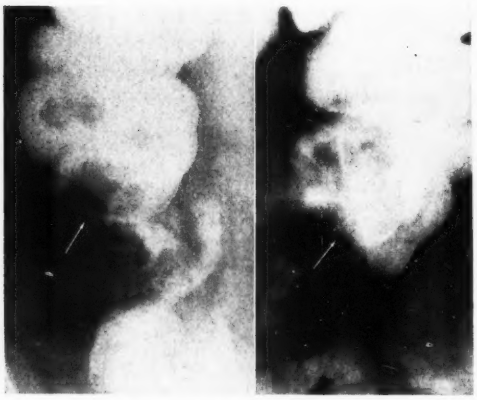

FIG. 1. Case 1. Barium enema demonstrating a filling defect in the cecum. The terminal ileum appears normal. The 4 previous barium enemas did not identify the lesion.

only clear liquids following the administration of castor oil.

If a lesion was suspected distal to the splenic flexure, the colonic washings were performed in the genupectoral position on the proctoscopic table, which was tilted head down to facilitate the flow of the irrigating solution and was subsequently tilted up to facilitate the recovery of the return fluid.

If a lesion was suspected proximal to the splenic flexure attempts were made to introduce at least 1.5 to 2.5 liters of warm irrigating solution depending on the patient's tolerance. It was administered slowly with the patient in a supine position. Varying the position of the patient, and massaging the abdomen promoted the distribution of the fluid throughout the colon and the distended cecum often could be palpated. After 10 minutes the return was collected by gravity drainage. In 5 cases the return was sparse; to increase its volume, 0.25 to 0.5 milligram of prostigmine was given intramuscularly, with good results.

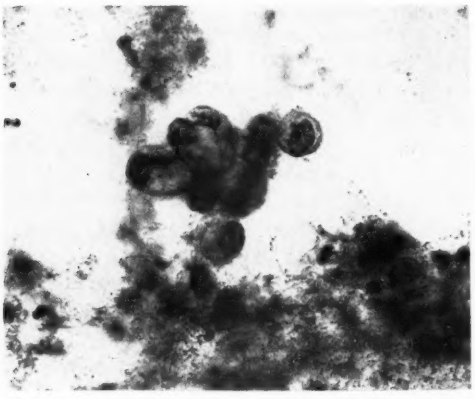

FIG. 2. Case 1. A single cytologic examination revealed adenocarcinoma cells. The diagnosis was confirmed at surgery. ×425.

Method I. Twenty patients were examined during the first 9 months of this study (October 1953 through June 1954). Only Ringer's solution was used as an irrigating fluid; the return was immediately searched for blood-tinged mucus and mucous shreds, which were smeared on slides thinly coated with Mayer's albumin, fixed in ether-alcohol and stained as described in a previous publication from this laboratory (5).

Method II. Forty-eight patients were examined during the last 9 months (July 1954 to March 1955) of this study. The initial rapid washing with Ringer's solution was followed by 500 to 1,000 cubic centimeters of acetate buffer with 14 to 21 milligrams of salt-free chymotrypsin enema which was retained for 5 to 10 minutes. The return was collected in iced containers and then was centrifuged at 5,000 revolutions per minute for 3 minutes. The sediment was smeared on slides thinly coated with Mayer's albumin. These were then fixed and stained as described in the foregoing.

RESULTS

In 16 of the 26 patients with colonic cancer a correct diagnosis was made by cytology (Table I).

Nine of the 26 patients were examined by method I (Table I). Malignant cells were recovered in 2 patients, 1 of whom had carcinoma of the cecum. In 7 patients malignant cells were not found on the first examination. In 1 patient malignant cells were recovered on a repeat examination 3 months later, following his recovery from a myocardial infarction.

FIG. 3. Case 3. Barium enema demonstrating multiple diverticula and a long segment of narrowing and irregularity of the sigmoid. The diagnosis of diverticulosis with diverticulitis was made by x-ray examination.

The remaining 17 patients with proved colonic cancers were examined by method II (Table I). Fourteen of these were correctly diagnosed by cytology. In 2 of the 14 the final x-ray diagnosis had been indecisive; and in 1 the correct diagnosis was not made prior to the fifth barium enema. Their case reports illustrate clearly the clinical usefulness of exfoliative cytology.

CASE 1. J. N., No. 313591, a 55 year old male, had experienced recurrent right lower abdominal quadrant pain, and a 16 pound weight loss during the past 2 years. Physical examination disclosed a prominent, puckered appendectomy scar and tenderness in the right lower quadrant. The hemoglobin was 11.7 grams per 100 cubic centimeters and the hematocrit 32 per cent. The stools gave a 4 plus benzidine reaction for occult blood. During a period of 29 days 5 roentgenograms of the colon were taken because the attending clinician suspected colonic carcinoma. The first 2 were performed in another institution. The first, second, and the fourth examinations revealed a cecal abnormality thought to be due to a benign lesion, though cecal carcinoma could not be ruled out. The third examination demonstrated no cecal abnormality. Polypoid carcinoma of the tip of the cecum was diagnosed on the fifth x-ray examination (Fig. 1). Cytologic examination, requested by the attending physician after the fourth barium enema, disclosed adenocarcinoma cells (Fig. 2). At operation a cecal carcinoma was found to be present, which was slightly nodular and almost entirely obliterated the tip of the cecum.

During the patient's evaluation 5 roentgen studies were necessary to identify the nature of a cecal deformity. Colonic exfoliative cytology established the correct diagnosis on a single examination.

CASE 2. N. K., No. 169451, a 64 year old white female, developed increasing constipation, cramping lower abdominal pains, and red blood in the stools for 3 weeks prior to hospitalization. The physical ex-

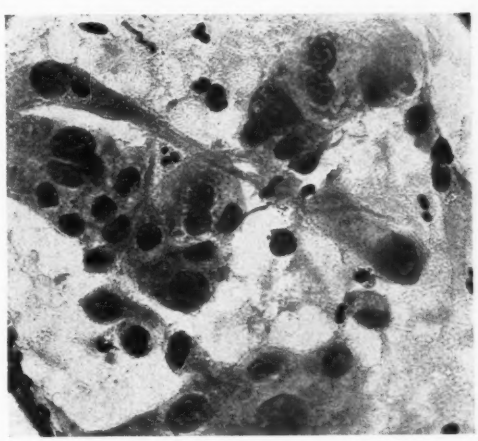

FIG. 4 Case 3. Colonic washing demonstrated unusually large malignant cells from metastatic ovarian carcinoma. ×425.

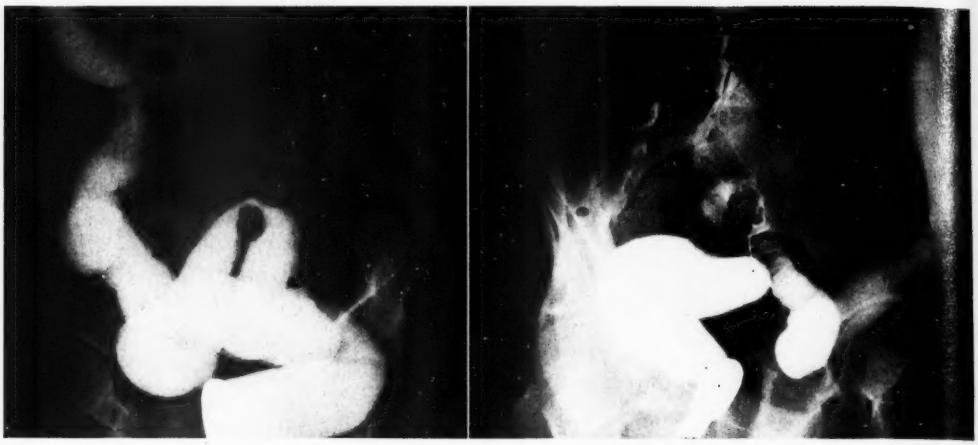

FIG. 5. Case 4. Repeated barium enemas demonstrated an "annular carcinoma of the sigmoid."

amination and routine laboratory data were unremarkable. Proctoscopy was normal to 20 centimeters. The barium enema demonstrated an obstruction in the midportion of the sigmoid colon but, in spite of multiple films, the lesion could not be visualized. Colonic cytology demonstrated carcinoma cells. At surgery, adenocarcinoma of the sigmoid was found virtually obstructing the lumen.

The obstructive nature of the lesion prevented adequate x-ray examination. The demonstration of malignant cells established the correct diagnosis.

CASE 3. K. P., No. 622348, a 61 year old white female, had been in excellent health until she developed watery and, at times, bloody diarrhea. This persisted for 3 months and led to hospitalization. The only pertinent finding on physical examination was an enlarged uterus which was continuous with a hard mass in the cul-de-sac. The routine laboratory data were not remarkable. The barium enema (Fig. 3) demonstrated diverticulosis and a "long segment of narrowing and irregularity in the sigmoid, with the appearance of diverticulitis. The possibility of a superimposed carcinoma could not be ruled out." On the smears numerous large and bizarre cells (Fig. 4) were seen, which did not resemble cells exfoliating from a colonic adenocarcinoma but were highly suggestive of metastatic cancer, probably of ovarian origin. At operation, an ovarian carcinoma (solid and cystic) was found. It had already metastasized to the colon, peritoneum, and liver.

Colonic exfoliative cytology provided the first evidence of the correct diagnosis by demonstrating ovarian carcinoma cells.

TABLE I.—COMPARISON OF DIAGNOSES BY X-RAY EXAMINATION AND EXFOLIATIVE CYTOLOGY IN 26 PATIENTS WITH MALIGNANT LESIONS OF THE COLON

		Cytology		*X-ray examination*		
	No. of patients	*Benign*	*Malignant*	*Benign*	*Indecisive*	*Malignant*
Method 1	9	7*	2	0	3	6
Method 2	17	3	14	0	2	15†
Combined	26	10	16	0	5	21†

*In 1 case colonic carcinoma was correctly diagnosed on the second examination.

†In 1 case the correct diagnosis was not made until the fifth barium enema.

No malignant cells were recovered by exfoliative cytology in any of the 32 patients who did not have colonic carcinomas. The final x-ray diagnoses in these 32 patients were: malignant lesion in 5 and indecisive in 10; the lesion was thought to be benign or no lesion was seen in 17. Subsequent surgery ruled out colonic carcinoma in 4 of the 5 patients in whom there was radiologic evidence of its presence. The fifth patient is well 8 months after examination.

The value of colonic exfoliative cytology in the absence of a malignant lesion is well demonstrated by the following case report.

CASE 4. J. W., No. 616410, a 37 year old white male, had recurrent episodes of abdominal distress due to duodenal ulcer during the past 9 years. Physical examination and routine laboratory data were unremarkable. On proctoscopic examination the mucosa was normal to 20 centimeters. Two gastroduodenal x-ray examinations showed marked deformity of the duodenal bulb and a crater in the second portion of the duodenum. On the basis of 2 barium enemas (Fig. 5) an annular carcinoma of the rectosig-

m d was diagnosed. The terminal ileum appeared no mal. Colonic washings revealed a large number of no nal columnar cells (Fig. 6). At surgery, regional en ritis was found involving the terminal 20 centi- m rs of the ileum. A fistulous tract was present be- tw n the diseased bowel and the sigmoid.

When a moderate to large number of nor- m l cells are recovered and no malignant c ls are seen, as in this case, there is strong ev dence for the benignity of the lesion ex mined.

n 1 additional patient malignant cells w e recovered and carcinoma of the sigmoid w s diagnosed by x-ray examination. The p ient thus far has refused surgery.

No malignant cells were recovered in the re aining 9 patients for whom no follow-up w s available.

DISCUSSION

The diagnosis of carcinoma in this study w s based only upon the demonstration of u equivocally malignant cells. There were n "suspicious" reports. If clear-cut cyto- lo ic malignancy was not evident on the sm ears, the case was reported as benign. In ou r experience, the reporting of suspicious c lls might give comfort to the cytologist, but it does not help the clinicians in establishing a diagnosis, which, in the final analysis, is the aim of any diagnostic method.

Hunter and Richardson found that colonic cells, both normal and neoplastic, are well preserved for a time in colonic mucus. In our experience, it was possible to recover well preserved malignant cells in blood-tinged mucus found in the colonic washings. However, relying on this source alone resulted in too many false negative reports. By method I only 2 of 9 malignant lesions were diagnosed on the first examination during the first 9 months of the study, and 1 of the remaining 7 in a repeat test.

By colonic exfoliative cytology malignant cells may be recovered from carcinomas of the cecum and the ascending colon. Four of 6 carcinomas in the right colon were diagnosed correctly (Table II). All 3 cecal carcinomas in this study were correctly diagnosed by cytology. It is of interest that in 2 of these the malignant cells were seen only on the smears of blood-tinged mucus; in the third case the diagnostic cells were recovered only in the centrifuged sediment obtained after the administration of prostigmine. Although occasionally well preserved diagnostic cells are found in blood-tinged mucus, particularly in the presence of fungating and bleeding carcinomas usually seen in the right colon, malignant cells are more consistently found in the centrifuged sediment.

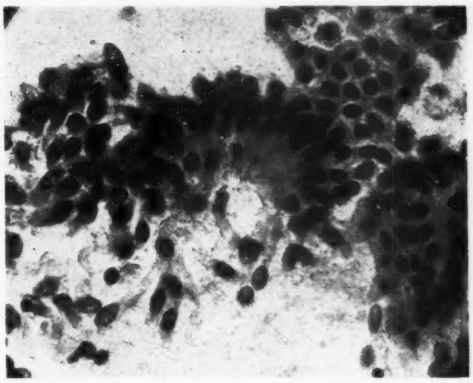

FIG. 6. Case 4. Cytologic examination revealed a large number of normal columnar cells. The operative diagnosis was regional enteritis with a fistula between the terminal ileum and the sigmoid colon. ×425.

The marked increase in diagnostic accuracy after July 1, 1954 (method II) coincided with 3 changes in technique. (1) The patient's preparation for colonic washing was more closely supervised and a 2 to 3 hour time lapse was maintained between the last cleansing enema and the examination. (2) During the examination the return fluid was kept cold and was promptly centrifuged after

TABLE II.—ANATOMIC LOCATION OF 26 COLONIC CARCINOMAS EXAMINED BY EXFOLIATIVE CYTOLOGY

Location	*Malignant cells not found*	*Malignant cells recovered*
Cecum	0	3
Ascending colon	2	1
Transverse colon	2	0
Descending colon	2	3
Sigmoid colon	4	8
Metastatic from ovary	0	1

gross fecal material, if any, was filtered off by a strainer. The sediment adhered well to the slides coated with Mayer's albumin. (3) The return of chymotrypsin-acetate buffer enemas often contained better preserved cells than those of Ringer's solution and at times it was the only source of malignant cells. At present our data are insufficient to evaluate adequately the usefulness of chymotrypsin in comparison with washing with the acetate buffer alone. This phase of the problem will require further study.

The most important single factor in the effective use of colonic exfoliative cytology is the proper preparation of the patient. The enemas should be given until the return fluid is clear. The frequent encouragement of the nursing service was essential in our experience to achieve this end. Whereas the cytologic recognition of malignant lesions of the colon is fairly simple, except in patients with chronic ulcerative colitis (3), the main difficulty lies in securing the malignant cells on the smears.

Obstructive lesions increase the difficulties in obtaining an adequately clean colon. In such cases particularly great care is required in preparation, but such lesions do not necessarily prevent the recovery of diagnostic cells. Malignant cells were obtained in 2 cases of sigmoid carcinoma completely obstructing the lumen.

The presence of malignant cells on the smears is conclusive evidence of a malignant lesion of the colon. On the other hand, the absence of malignant cells in colonic washings does not rule out colonic carcinoma. However, since tumor cells exfoliate at a higher rate than normal ones, the recovery of a large number of normal columnar cells in the absence of malignant ones (as was demonstrated in Case 4) is very strong evidence against malignancy in the lesion examined.

In experienced hands, colonic exfoliative cytology is a reliable and valuable diagnostic adjunct in the identification of primary and metastatic colonic malignancy if it involves the mucosa. Adequate preparation of a cooperative patient, in whom a colonic lesion is suspected, could very well take place at the home and the examination can be performed on an outpatient basis. However, the cumbersome nature of the present type of preparation will prevent colonic exfoliative cytology from becoming a mass screening procedure for the detection of colonic malignancy beyond the reach of the proctoscope.

SUMMARY

Colonic exfoliative cytology was performed in 68 patients during an 18 month period. Follow-up information was available in 59 cases.

In 26 cases malignant lesions were found at operation. The correct diagnosis was established by colonic exfoliative cytology in 16 patients. There was a marked increase in the diagnostic accuracy of the method during the last 9 months of the study following changes in technique.

A case of metastatic ovarian carcinoma was correctly diagnosed by cytology.

One patient in whom malignant cells were found and in whom carcinoma of the sigmoid was diagnosed by x-ray study has refused surgery.

There were no false positive reports in 32 cases in which malignancy was excluded (by surgery in 14 and by clinical observation in 18 cases).

Nine patients in whom no malignant cells were found could not be reached for follow-up.

CONCLUSION

Colonic exfoliative cytology, in experienced hands, is a valuable adjunct in the diagnosis of colonic lesions. The demonstration of malignant cells is conclusive evidence for carcinoma, although their absence does not exclude its presence.

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OBSERVATIONS ON THE MECHANISM OF BRAIN CONCUSSION, CONTUSION, AND LACERATION

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INVESTIGATORS during the past 75 years have observed that in the experimental animal the extent of medullary and brain stem involvement determines the severity of the head injury. Thus, Duret, Polis, Denny-Brown and Russell, Gurdjian and Webster (6), Walker, Kollros, and Case, and others have pointed out that death of the experimental animal is often the result of the physiologic abnormalities which are due to brain stem damage. Windle, Groat, and Fox have shown in microscopic study of the brain that the degree of abnormality of the cells increased with the severity of impact. This was particularly true in the brain stem and medullary areas. In human experience it has been shown that small hemorrhages in the brain stem accompany profound head injury. Many years ago Duret concluded that such hemorrhages may result from the transfer of energy along the cerebrospinal fluid pathways. Among others, Wycis, however, has recently found that the removal of the cerebrospinal fluid in the experimental animal did not stop concussive effects, in fact, such effects were as readily or more readily obtained under these circumstances.

Cerebral anoxia has frequently been presented in the past as the possible cause for the initial unconsciousness following an impact. Studies of the phosphorylation metabolites and the level of lactic acid in the frozen brain tissue have shown conclusively that no evidence of anoxia was present for periods up to 80 seconds following the time of impact (5). The occurrence of unconsciousness following an injury is so rapid that the possibility of an anoxic cause is precluded. The more recent investigators have concluded that the physiologic abnormalities following head trauma are the result of mechanical forces acting upon the intracranial contents.

The subject of cerebral concussion has been discussed repeatedly since the case of "fatal concussion" reported by Littré many years ago. Littré was the exponent of the theory that concussion is a state of unconsciousness following head trauma unassociated with lesions of the nervous system. His celebrated case was interesting not only because it initiated a new concept in head injury but his concept was also based upon unsubstantiated data. In fact, a complete autopsy was not performed on the patient who died instantly after running head first into a wall. The possibility of spinal cord damage from involvement of the craniospinal junction apparently was not investigated. Since the time of Littré and Petit, concussion has been defined as a posttraumatic state usually associated with unconsciousness, slow pulse, and the pallor of a shock-like state but with no visible lesions of the nervous system. In a recent paper by Denny-Brown and Russell this definition has been supported.

There has been a tendency through the past three centuries to consider cerebral concussion as less severe while brain contusion and laceration have been considered as a more severe involvement of the nervous system. Many investigators have noted, however, that in animal experiments as well as in the human, extensive lacerations of the brain may occur with no associated initial

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Aided by the Kresge Foundation.

u consciousness. Portions of the skull and b ain may be damaged and even evulsed w thout the patient losing consciousness.

With the information available at present it can be stated that concussion exists only w en the upper brain stem is sufficiently in- v lved by the injury. Brain contusions and l erations may occur without concussion if th brain stem is relatively spared. If con- t ions and lacerations occur in the brain st m, a severe or fatal head injury is usually p sent.

T E MECHANICS OF HEAD INJURY AND CERTAIN E PERIMENTAL AND CLINICAL OBSERVATIONS

The head may be subjected to direct or i lirect injuries. In a direct injury a moving o ject contacts the nonmoving or slower n oving head. Such objects may be a ham- n r, brick, stone, bullet, or other missiles w ich may or may not cause penetrating w unds. In an indirect injury to the head th e moving head and body may come in con- t t with a nonmoving or slower moving ob ject resulting in rapid deceleration of the skull and contents. For instance, the body may fall from a height to the ground and strike on the lower extremities and buttocks. The head is then thrust downward toward the spinal column. This may result in a circular fracture about the foramen magnum. In some instances there may be actual penetration of the upper end of the spinal column into the skull. Other indirect injuries include the "whip lash" injuries of the head and neck and certain falls in which other parts of the body contact the ground before the head does.

In direct impact the size and shape of the injuring object may also be significant. A sharp object of small size such as a stiletto may tear through scalp, skull, and brain if it is thrust with high speed, without causing loss of consciousness. Small light objects traveling at high velocity may strike the head and because of their small kinetic energy may produce no injury. Large masses moving with very low velocity may compress the head with mashing and squashing

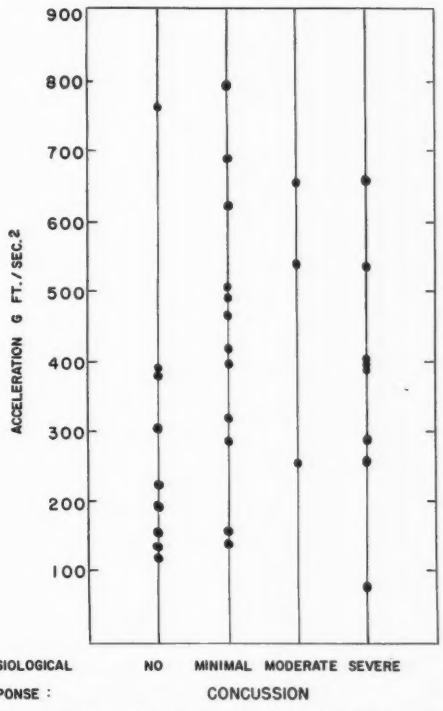

FIG. 1. Relationship between acceleration and degree of cerebral concussion. Note that high levels of acceleration were recorded with no effects. There was no correlation between the level of acceleration and a concussive effect.

of its contents if their kinetic energy is of sufficient magnitude.

As a result of forces produced by either direct or indirect injuries the following basic mechanical effects occur: the head is suddenly set into motion (accelerated); the head is suddenly stopped (decelerated); or the head is compressed and deformed with resultant squeezing of the contents. Acceleration and compression frequently coexist as do also deceleration and compression. There has been a tendency to consider dynamic compression injuries as being different from acceleration or deceleration injuries. That acceleration or deceleration cannot exist without some dynamic compression must be admitted. In dynamic compression injuries, the head may be more fixed than in injuries

in which deceleration or acceleration is predominant. With almost all dynamic compression injuries, however, some portion of the head is accelerated or decelerated.

Acceleration, deceleration, and compression may cause the following physical effects on the head and contents: (1) deformation of the skull producing compression of the contents due to decrease in volume; (2) a sudden increase in intracranial pressure at the time of impact; (3) mass movements of the intracranial contents; (4) distortion of the skull and the dural septa; (5) shearing off of a portion of the head and contents without necessarily producing an increase in intracranial pressure at the time of impact; and (6) shearing and tearing with high levels of increased intracranial pressure such as occur in bullet and shell fragment wounds. Combinations of such effects may occur in certain types of injuries. These various effects of injury will be discussed in the next few paragraphs.

Deformation of the skull has been studied by the stresscoat and the strain gauge techniques. Depending upon the velocity and energy of the blow, there may be an elastic deformation at the point of impact. Following the impact, the skull, which is bent inward, tends to return to its normal position. With higher velocity blows there may be a perforation or depression at the point of impact due to failure of the bone from extensive deformation. The higher the velocity the more localized is the area of deformation except in extremely high velocities which may cause extensive shattering due to secondary action of the contents. Depressed fractures and penetrating fractures occur at the point of impact. However, linear fractures of the skull are due to tensile stresses[1] at some distance from the area of impact and to the outbending of the skull rather than inbending. With deformation of the head due to a blow there will be some compression of the contents with a resultant increase in intracranial pressure from this deformation. If the deformation is so severe as to cause failure with depression and fragmentation of the bone at the point of impact, there may be tearing of the membranes of the brain and of the brain itself. Contusions and lacerations due to depressed fractures are, of course, commonly observed.

A sudden increase in intracranial pressure at the time of impact has been observed and is due to acceleration or deceleration of the head and also to deformation of the skull at the point of impact. In experimental work previously reported it has been shown that the level of the pressure and its time duration are important in the production of the clinical effects. The higher the level of pressure the shorter the time duration required to result in an effect similar to that produced by a lower pressure lasting for a longer period of time. It has been shown that pressures of 750 to 5,000 millimeters of mercury or more cause concussive effects. A definite correlation between the level of pressure and its time duration with the clinical effects has been observed in blunt injuries to the heads of dogs.

Acceleration of the head due to hammer blows was studied with the use of the unbonded wire accelerometer[2] (Statham) and the barium titanate[3] accelerometer. The Statham accelerometer records the magnitude and the time duration of the acceleration while the barium titanate accelerometer only indicates the magnitude of the acceleration. The records of maximum acceleration

[1]Tension or tensile stress is defined as a tearing apart force.
Compression may be defined as the state of being squeezed or being pushed together.
Shear or shear strain results in tearing of material or tissues due to twisting or sliding of certain parts over others.
Stress is the force acting per unit of area.
Strain is a deformation accompanying stress.

[2]The unbonded wire accelerometer acts by straining a number of fine wires 1/1,000 inch in diameter by means of a mass attached to them. The electrical resistance of the wire varies directly with the strain which is in turn proportional to the acceleration applied to the attached mass. The change in resistance is determined by means of a Wheatstone bridge circuit. This type of accelerometer responds to both transient and steady state phenomena. It permits recording of the time duration of the acceleration.

[3]The barium titanate is a crystal in which a potential difference is produced across its faces when it is deformed, the amount of potential difference or voltage being proportional to the degree of deformation. The crystal is mounted in such a manner that its deformation is proportional to the acceleration to which it is subjected. The potential difference exists only during the period in which the deformation is undergoing variation. It does not provide indication for steady state conditions.

from both of these acclerometers are comparable (7). By the use of these techniques it has been found that the degree of the concussive effect was not directly related to the magnitude of the acceleration. In some cases evidences of severe clinical effects were noted with low accelerations and in other cases no concussive effects were noted with high accelerations (Fig. 1). It must be admitted, however, that in experiments with hammer blows to the exposed skull there is a greater possibility of compression of the skull than if the scalp were intact over the area of blow. Acceleration and deceleration produce clinical effects by causing increase in pressure of the intracranial contents and this pressure increase in turn causes the injurious effects.

When the intracranial pressure is recorded at impact from both sides of the head, a variation on the two sides is noted. The pressure is higher on the side of the blow than it is on the opposite side. In other words, pressure gradients exist because of the dynamic condition resulting from the blow. These pressure gradients last for the duration of the acceleration.[4]

It may be worth while to orient certain anatomic characteristics of the head to this problem. The skull is a spheroid structure containing semiliquid contents including brain, blood, and cerebrospinal fluid. This closed cavity feature of the head is a major consideration. The cavity of the head is solidly supported by bone. The cranial dura is intimately attached to the inner layer of the bone. At the craniospinal junction, however, the cranial contents become continuous with the spinal cord which is encased in a canal where dura and bone are not as intimately apposed as in the skull cavity. In the spinal canal large vertebral veins and fatty tissue are found between the dura and bony structure. This bony structure is not continuous. The ligamenta flava between laminae and intervertebral foramina for the passage of nerves and blood vessels are areas in which large deformations can occur. These deformations tend to prevent a pressure build up in the spinal canal. Thus a sudden increase in intracranial pressure results in pressure gradients through the region of the brain stem and cerebellum in the direction of the foramen magnum. This pressure gradient produces shear strains throughout the region in which it acts, the magnitude of the shear strains being proportional to both the magnitude of the pressure gradient and its time duration. The effect of

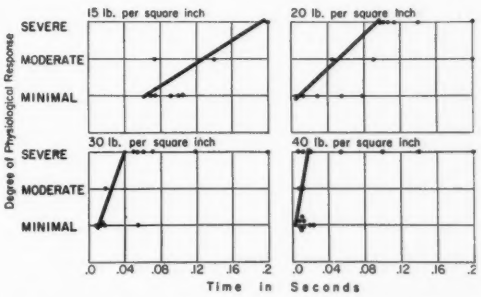

FIG. 2. The time duration and the level of the pressure are important in the effects obtained. With higher pressures for shorter periods of time the effects were similar to those due to lower pressures for longer time periods.

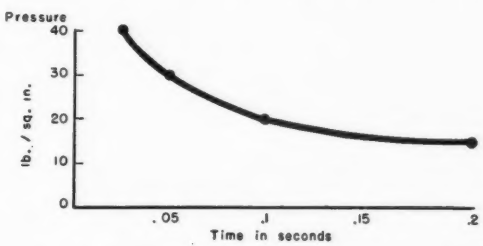

FIG. 3. Pressure and time correlation in cases with severe concussive effects. The higher the level of the pressure used the lower the time duration in order to effect a severe result.

[4] A pressure wave travels at the approximate rate of 4,700 feet per second through the intracranial contents. This is computed from the expression $V=\sqrt{E/P}$. V represents the velocity, E the bulk modulus of elasticity, and P the mass density. For saline solution E=310,000 pounds per square inch and the mass density or P=.0362/384. Consequently $V=\sqrt{\frac{310,000}{(.0362)}}=57,300$ inches per second or 4,700 feet per second.

Strain and stress travel through compact bone at a velocity of 8,860 feet per second. This is determined by the same expression as above, $V=\sqrt{E/P}$. For bone E is 2,000,000 pounds per square inch and the mass density or $P=\frac{.06922}{384}$. For compact bone this expression becomes $V=\sqrt{\frac{2,000,000}{(0.6922)}}=106,000$ inches per second or 8,860 feet per second.

this pressure gradient differs from that produced by, and in the direction of the acceleration in that in the latter case all elements of the brain are essentially in dynamic equilibrium due to the action of inertia forces. If this dynamic equilibrium were perfect, no shearing strains would be produced because of this pressure gradient. Since the skull deforms with the blow, however, some shear strain will exist throughout the cranial cavity, but its magnitude will not be comparable to that in the region above the craniospinal junction because of the unbalanced pressure gradient through this area.

In experiments recording accelerations and increased intracranial pressure, reported elsewhere (4), a concussive effect[5] could not be related to the magnitude of the acceleration alone since high accelerations failed to produce concussion in certain animals while low accelerations produced concussion in others. As previously stated one of the difficulties in these tests was that in some instances hammer blows produced deformation of a degree severe enough to cause failure of the bone, so that increased intracranial pressure from the latter cause could not be separated from that produced by the acceleration.

In order to eliminate the latter variable, experiments were performed by applying an air pressure pulse directly to the unopened dural sac for various time periods from 0.1 to 0.001 of a second. The magnitude of the pressure pulse was varied from 15 to 100 pounds per square inch. These experiments indicated clearly that the magnitude of the pressure alone did not determine the concussive effect but that its time duration was also significant. A low pressure lasting for a longer period (0.1 of a second) gave the same type of physiologic response of blood pressure and respiration as a high pressure lasting a short period (.001 of a second). Even more convincing are the records shown in the accompanying figures which describe the results of experiments with pressure applied at certain constant magnitudes but with varying time durations. Thus, 15, 20, 30, and 40 pounds per square inch were applied to the intact dural sac for the indicated time durations. By increasing the time duration of the pressure relatively, more serious effects were produced. With higher levels of pressure serious effects were obtained in shorter time periods (Figs. 2 and 3).

In blunt injuries of the head when major distortion of the skull and contents does not take place and when extensive failure of bone is not present, the effects of the blow are due principally to a sudden increase in intracranial pressure at the time of impact. This increase in pressure may be of the order of 750 to 5,000 millimeters of mercury or 15 to 100 or more pounds per square inch. These changes in pressure are caused by the deformation of the skull and acceleration or deceleration of the head due to the impact. The area which receives the most injury under these circumstances is the neural tissue in the vicinity of the craniospinal junction or the brain stem. The shear strain produced in this region is a function not only of the magnitude of the pressure but also of its time duration (Figs. 4 and 5).

Microscopic work in progress at the present time reveals that cellular changes occur in the brain stem and medulla with the application of a pressure pulse definitely below levels causing a concussive effect. Thus injuries too mild to cause a measurable concussive effect, nevertheless, produce cellular changes which may explain certain reversible posttraumatic states seen in the human.

Mass movements of the intracranial contents may occur at impact. Mass movements are caused by differences in the rate of acceleration of the skull and its contents. They may

[5]In experimental work (under morphine analgesia or pentothal anesthesia) minimal concussion is associated with a short apnea and a small rise or fall of blood pressure following impact. A moderate concussion is characterized by an apnea of 15 to 60 seconds and a brisk rise of blood pressure of 40 to 100 millimeters of mercury. Respirations and blood pressure return to normal levels in about 3 minutes. In a severe concussion respirations cease, almost always permanently, and there is a steep rise of blood pressure which goes down to zero in 5 to 15 minutes. A severe concussion nearly always is fatal. A minimal concussion as defined is probably more severe than the usual reversible concussion seen in the human.

FIG. 4.

FIG. 5.

FIGS. 4 and 5. Photographs of brain of a man who was struck by an automobile and was dead on admission to the hospital. There was no skull fracture at autopsy. The brain externally appeared normal. There was a hematoma of the left chest from fractured ribs. Section of the brain revealed hemorrhages extending down from the upper portions of the brain stem to the medulla. These findings are similar to those noted in experimental animals after a severe blunt head injury.

be due to the linear or angular accelerations. Acceleration and deceleration injuries are apt to be associated with mass movements of the intracranial contents. Angular acceleration may result in shear and tear of tissues as well as compression with contusions of the brain. When the head is free to move, an object of small size striking the head may not possess sufficient energy to accelerate the head and cause mass movements but with adequate mass, acceleration occurs. The work of Pudenz and Sheldon with cinephotography has conclusively visualized the mass movements occurring at impact. Mass movements result in tearing of tissues, particularly when the brain and irregularly formed cranial bony structures are apposed such as at the floor of the anterior third of the skull, the middle fossa, and the lesser wing of the sphenoid in their relationships to the frontal and temporal lobes of the hemispheres (Fig. 6). The sharp edges of the tentorium may tear the brain stem (Fig. 7). The corpus callosum may be contused by the impact of the free edge of the falx cerebri. Many contusions and lacerations of the frontal and temporal lobes unilaterally or bilaterally are caused by mass movements of the brain against the rough and irregular anterior fossae and the knife-like edge of the sphenoid ridge. These concepts were enunciated rather clearly in the writings of Prescott Hewitt in 1861. LeCount and Apfelbach have also shown conclusively that acceleration and deceleration injuries may be associated with extensive contusions of the brain surface (Fig. 7).

Contrecoup injuries of the surface of the brain may be ascribed to mass movements or to cavitation[6] and below normal pressures

[6]Cavitation is the name given to the phenomenon of bubble formation and collapse of bubbles in an area of suddenly reduced pressure, in a liquid. The bubbles are formed as parts of the fluid change from a liquid to a gaseous state in the region of reduced pressure. Damage is caused as the bubbles collapse since large forces are produced by the collapse.

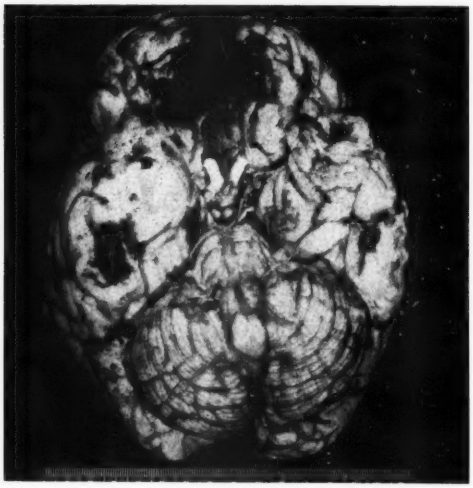

FIG. 6. Contusions of the temporal and frontal lobes resulting from mass movements. The greatest majority of bruises in autopsy cases are found in these positions, shown in Figure 7.

in regions diametrically opposite to the area of impact where the pressure is definitely increased at the time of impact. The cavitation effect is most probably caused by the breaking of molecular bonds of adhesion and cohesion due to a reduction of pressure. Cavitation and below normal pressures may then result in tensile forces in the tissues with contusions and hemorrhages in an area opposite to the site of impact. With either frontal or occipital skull impacts, contusions of the inferior surfaces of the frontal and temporal lobes of the hemispheres occur with almost equal frequency. In a certain number the cause of these contusions is the intimate apposition of the brain and bone resulting in a crowding of the frontal and temporal lobes of the hemispheres against the forward portions of the skull. With occipital blows the subfrontal and temporal contusions may either result from below normal pressures in the forward portions of the cranial cavity or from the "bouncing back" of the cranial contents toward the irregularly formed anterior and middle fossae with resultant tears. The occipital and posterior portions of the cerebrum are encased in a smooth lined area of bone and dura including the tentorium cerebelli which provides a damping effect for certain injuries. Therefore, bouncing back or the crowding of the brain in this direction will result in fewer contusions (Fig. 7).

In discussing the mechanism of contrecoup lesions, Goggio suggests pressure gradients as the cause of such lesions. As already stated, below normal pressures may cause some lesions but abutment of the brain against rough and irregular bony structures is the most frequent cause of these contusions.

Distortions of the skull and dural septa may occur in craniocerebral trauma (Fig. 7) with forces acting upon the head with little or no velocity. In injuries to the newborn in the birth canal, the forces being applied to the head with the contractions of the uterus and the resistance of the birth canal may result in distortion of the head, tear of the dural septa, tears of the brain, and venous sinuses as well as blood vessels in the substance of the brain. Brain stem damage by distortion of the bony parts, septa, and dural lining occurs. Distortions of the head may also occur in the adult as a result of very low velocity blows of great magnitude, such as when the head is caught between the bottom of a car and the ground when a jack lift suddenly disengages. Concussion results only when the brain stem is injured in such cases.

Shearing off of a portion of the head and contents occurring with little or no increase in intracranial pressure at the time of impact may be illustrated by sword wounds, puncture wounds by a sharp object, and certain wounds by shell fragments and bullets. In some open wounds of the head with portions of the head and contents severely lacerated there may be no initial unconsciousness. In such cases the closed cavity hydrodynamics of the head is disturbed and the essential pressure gradients do not develop or may not last long enough to cause a derangement of the brain stem centers. Thus, extensive damage to the brain without unconsciousness may occur in this class of cerebral injury.

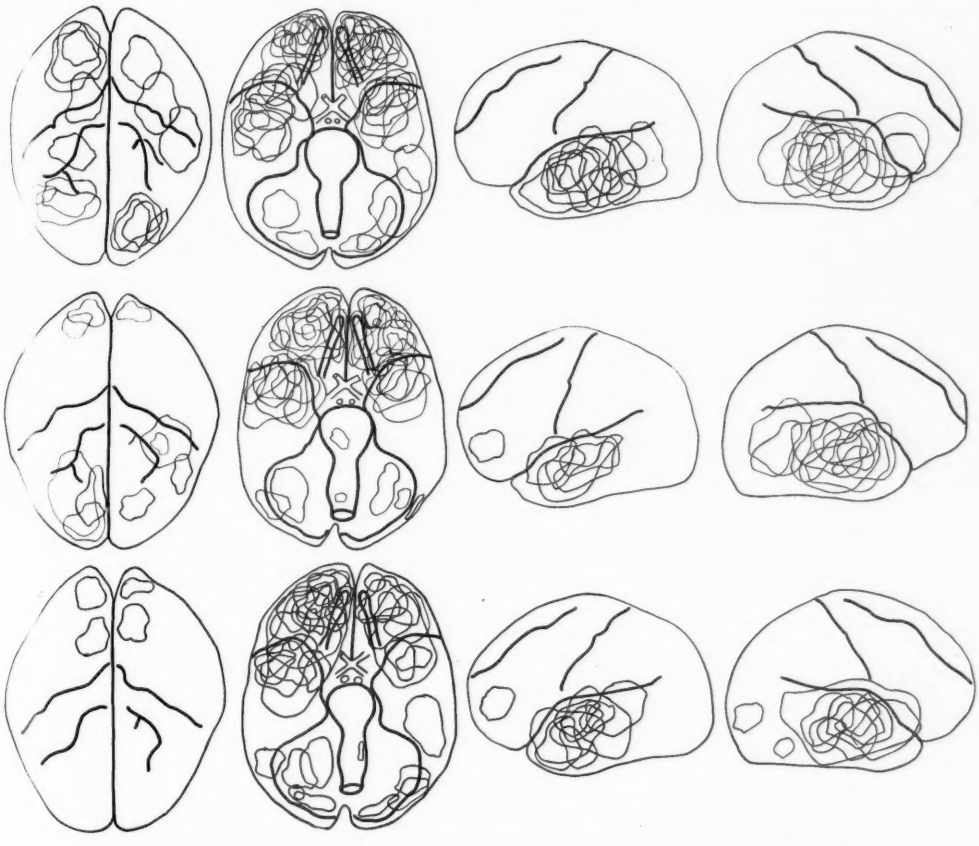

FIG. 7. A composite view of 189 contusions in 152 consecutively autopsied cases of head injury. The majority were in the frontal and temporal tips and the inferior surfaces of the frontal and temporal lobes. There were three contusions of the brain stem. One contusion involving the upper brain stem was probably caused by the impact of the incisural border of the tentorium cerebelli. Note that contusions are few in the posterior portions of the hemispheres since the occipital lobes are protected by the soft tentorium cerebelli inferiorly and the smooth dura bone lining of the parieto-occipital region of the head.

Shearing of a portion of the head and contents with extreme increase in intracranial pressure is associated with bullet and some shell fragment wounds. As the missile passes through the brain there is a great increase in intracranial pressure caused by a "temporary cavitation" about the missile. This may cause profound brain stem involvement provided that there is not a disturbance of the closed cavity hydrodynamics as in the tangential wounds of the brain and in certain of the frontal wounds associated with extensive fragmentation of the bone overlying the area of damage (bursting fracture). In the greatest majority, however, with a high velocity wound death is inevitable because of an involvement of the brain stem. With lower velocity missiles of smaller mass such as with a pistol (.22 caliber) there may be a greater likelihood of less severe damage to the brain stem.

The cavitation about the missile also results in a circumscribed destruction of tissue. Consequently with higher velocity wounds,

there is a core of devitalized tissue which is more extensive than in the lower velocity penetrating injuries.

DISCUSSION

Damage to neural tissues in head injuries may take place by one of three mechanisms: (1) by pushing the tissues together or compression; (2) by tension or tearing apart of the tissues; and (3) by shear or twisting when portions of the tissues are slid over other portions resulting in tearing. All of these mechanisms may operate. The scalp will be compressed or mashed under the point of the blow. It rotation of the head occurs, portions of the brain may be injured by abuting against bone projections within the skull, thus being compressed. Other portions may be torn because of tension produced as the brain rotates with respect to the skull, and finally shear may occur because of cavitation and pressure gradients, the latter occurring principally in the region of the brain stem.

Contusions and lacerations may result from several causes: inbending of bone at the area of impact with tearing and bruising of tissue by depressed fragments; cavitation and below normal pressure in a region opposite to the area of impact producing contrecoup lesions; mass movements of the brain against bony irregularities such as the anterior and middle fossae; distortion of the skull and tears of brain from deformations of dural septa and meningeal attachments to the brain; shear between attached areas and moving brain with resultant tears of connecting veins; tears of tissue from shear due to pressure gradients in the cranial cavity.

Contusions and lacerations of the brain and tears of intracranial tissue may occur without unconsciousness. An example is intracerebral hematoma, due to a bruise, without an initial loss of consciousness. Another example is chronic subdural hematoma when mass movements may cause tear of connecting veins with resultant hematoma unassociated at the time of injury with any changes in the conscious state. Evidences of increased intracranial pressure in such cases may occur several weeks later as the clot enlarges because of its physical chemical properties (increased osmotic pressure).

The mechanism causing unconsciousness following an impact is not clearly understood. There is increasing evidence to show that the reticular formation of the high brain stem, the periaqueductal grey matter, and the posterior portions of the thalamus and hypothalamus are the regions in which an arousal or conscious state may be mediated. An involvement of this area by a blow may result in a depression of function in these cells causing an unconsciousness. It is thought that cellular depression of activity in this neighborhood is the cause of the unconsciousness associated with anesthetic agents. The pacemaker mechanism of the brain for electrical activity resides in the reticular area of the brain stem and midbrain and this area is believed to be responsible for the rhythmic electrical emanations. Without its activity there occurs disorganization of the electrical pattern of the cortex. It has also been observed that in the human under local anesthesia, compression of the neighborhood of the posterior hypothalamus and the brain stem region causes an unconsciousness associated with deep snoring. Many surgeons believe that the area of consciousness is probably in the brain stem and the posterior hypothalamus. This is not to say that the higher centers do not influence consciousness. With visual and auditory impulses, the speech center and the frontal and limbic lobe regions, the so-called conscious human being is made to respond to his environment according to his ability to assess the incoming afferent impulses. The state of akinetic mutism, the aphasic state, the peculiar behavioristic abnormalities of the lobotomized individual are all variations of consciousness denoting a stripping of supranuclear influences which form the normal pattern of the conscious state.

Our information suggests that cerebral concussion is due to an involvement of the cells in the brain stem resulting in reversible

or irreversible changes associated with unconsciousness; these changes at times may be of a degree to cause respiratory, vasomotor paralysis, and death. On the other hand, they may be mild enough to permit recovery completely from the effects of the blow. In association with an involvement of this region the vasomotor abnormalities frequently seen in concussive blows, pallor with peripheral vasoconstriction, and splanchnic dilatation are undoubtedly due to hypothalamic influences for the preservation of the organism.

The brain stem may be involved not only by blows but also by other reflex and psychic factors. Reflex cortical mechanisms may cause a depression of this region resulting in an unconsciousness due to visual, olfactory, and auditory stimuli related to horror and fright. The effect of a relative cerebral anemia of the brain from vasodilation in the splanchnic region may result in an unconscious state due to sudden decreased blood flow to this region as well as to other parts of the brain. Reflex effects, such as from a solar plexus blow or a blow upon the neck resulting in a derangement of the vagoglossopharyngeal connections, may also involve these centers with depression of the cells and resultant unconsciousness or semiconsciousness or faintness. Labyrinthine injury may result in impulses extending toward this region causing a disturbed conscious state, as may often be seen in boxers acutely disabled by a blow to the head or jaw.

A concussive effect may be associated with injuries elsewhere in the cranial cavity with tears and bruises or it may be unassociated with macroscopic brain damage. In other instances the brain may be penetrated by a knife blade, hammer, or shell fragment, without associated unconsciousness. Frontal portions of the brain may be completely destroyed with laceration and tearing of brain tissue without unconsciousness. Under local anesthesia the brain may be surgically damaged and consciousness may not be affected.

CONCLUSION

1. Cerebral concussion is an acute posttraumatic state associated with unconsciousness, pallor, and a shock-like state and is the result of derangement in function of the brain stem. The brain stem involvement may be of varying degree involving both reversible or irreversible damage. The reversible state may result in complete recovery; the irreversible, in unconsciousness with ultimate death. Concussion may be associated with brain contusions and lacerations or it may be unaccompanied by macroscopic evidences of injury to the neural tissue. Contusions and lacerations of the brain may be unaccompanied by concussion.

2. The closed cavity dynamics of the head may be disturbed by injuries resulting in major damage with or without concussion. The closed cavity dynamics in many injuries is the cause of unconsciousness and death. Both are due to physical forces deranging the brain stem function. Concussion occurs as a result of brain stem injury either from increased intracranial pressure at the time of impact, direct injury by distortion, mass movement, shearing, or destruction by a missile.

3. The terms cerebral concussion, contusion, and laceration should not be used to denote varying degrees of nervous system damage, with concussion identified as representing the mildest form. The evidence indicates that concussion is due to an involvement of a specific area in the brain, namely the brain stem. A contusion or laceration in this area may be fatal. However, contusions and lacerations in other portions of the nervous system may be present with no associated concussive effect if the brain stem area is not sufficiently involved.

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THE ROLE OF SEROTONIN IN EXPERIMENTAL PULMONARY EMBOLISM

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IT IS OFTEN NOTED that the general effects of pulmonary embolism far exceed those that might be expected from the size of the embolus.

For example, an embolus which is shown by the subsequent clinical progress to have been a small one may produce marked circulatory collapse and a sense of impending death. While massive embolism may cause death by mechanical blockage of the pulmonary artery, the actual mechanical effects of smaller emboli must often be less in view of the extensive nature of the lung bed. To account for the discrepancy between the symptoms observed, the size of the embolus and the area of the lung bed affected, various authors have blamed the group of depressor reflexes which may be elicited from the lung vessels themselves.

While there is extensive evidence that these reflexes play a role in pulmonary embolism, there are few references to the influence of a humoral factor other than histamine, released from damaged cells, as a possible cause of the shock which is present in this condition.

For many years it has been noted that clotting blood releases a humoral substance which is capable of producing severe cardiovascular depression. The active principle, serotonin (5-hydroxytryptamine) was isolated by Rapport in 1948. Zucker has suggested that it is freely released by thrombin during the clotting process. More recently Biorck and his associates, Branwood and Bain, Thorson and his co-workers, and Isler and Hedinger have shown that serotonin is also secreted from argentaffin tumors in human cases. Many of the circulatory symptoms which these cases present resemble those occurring in cases of pulmonary embolism. The circulatory effects, presumably due to the serotonin secreted by such tumors, have been, moreover, investigated experimentally by Reid, Comroe and his associates, Mott and Paintal, Ginzel and Kottegoda, Dames and Comroe, and Kottegoda and Mott. According to these workers, the circulatory effects of serotonin are caused by constriction of the coronary vessels, by excitation of the coronary chemoreflex, by activating reflexes from atrium and great vessels in the thorax, by stimulating afferent and carotid sinus, baroreceptors and chemoreceptors, vagal fibers, and by a direct constrictor action on the great veins, trachea, and bronchi themselves.

The purpose of the present article is to demonstrate that, while many active agents are released from clotting blood, the signs and symptoms of experimental pulmonary embolism may depend on the release to some considerable extent of serotonin from both the blood clot and the infarcted area of lung.

METHODS

Thirty-two cats of 2 to 4 kilogram body weight were anesthetized with chloralose administered intraperitoneally, 80 milligrams per kilogram of body weight. Tracheotomy was performed and the external jugular or common femoral vein was then cannulated to allow blood samples to be withdrawn and substances to be injected. Arterial blood pressure was recorded from a cannula in

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Work done during tenure of a Fellowship from the Medical Research Council.

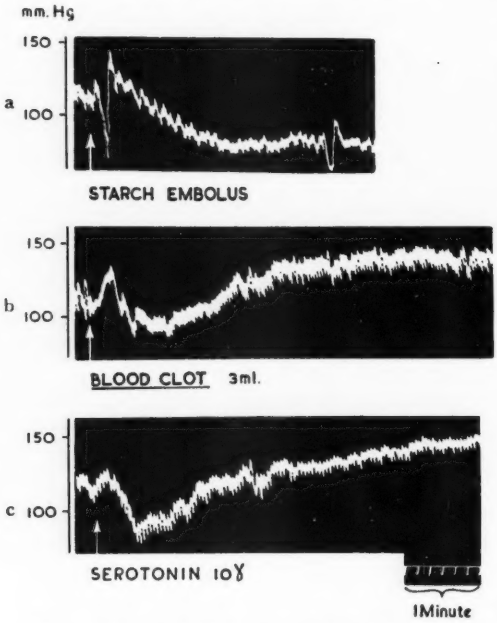

FIG. 1. The effect on the systemic arterial pressure of a cat, obtained by injecting: a, starch suspension; b, blood clot suspension; c, serotonin, into the femoral vein.

the right common carotid artery connected to a mercury float manometer writing on a smoked drum.

At the beginning of each experiment 8 milliliters of blood were removed from the venous side of the circulation and this was subsequently divided into four lots: (1) 2 milliliters of blood were allowed to clot and the serum was separated by centrifugation at 3,000 revolutions per minute; (2) 2 milliliters of blood were admixed with the disodium salt of ethylene diamine tetraacetic acid in concentration of 0.1 per cent (for purposes of platelet protection from disruption), and heparin 1 drop of 5,000 international units per milliliter of solution was added, in siliconed vessels; (3 and 4) double samples of 2 milliliters of blood were each taken and spread in a thin film on a glass plate, sealed to prevent drying and allowed to clot spontaneously. After a period of approximately 1 hour, the clot was chopped up to fragments of an average size of 2 millimeters in diameter and suspended in 1 to 2 milliliters of normal saline for injection intravenously. With this size of fragment, distal impaction in the pulmonary arterial bed occurred in all cases.

Assays for the serotonin content of plasma serum and blood extracts made according to the method of Toh were performed on the rat colon preparation by Feldberg and Toh in 1953, suspended in a 20 milliliter bath. Assays were also made on the guinea pig's ileum treated with atropine and mepyramine in concentrations of 1:10-7 respectively.

Mechanical embolization was effected by a suspension 1:4 of potato starch granules in normal saline; the average size of these emboli was 90 microns.

Pulmonary arterial pressures were recorded in several experiments. Two techniques were used. In one the artery of the lower lobe of the left lung was cannulated and the pressure recorded on a mercury manometer, with a float writing on a smoked drum. When this method was used, systemic arterial pressure was recorded on the same trace simultaneously. In the other method, pressures were recorded on a capacitance manometer, and simultaneous electrocardiographic readings were taken. Respiration was maintained in both cases by means of a Brodie-Starling pump after thoracotomy through the fourth left interspace.

Drugs were administered as follows: serotonin as 5-hydroxytryptamine creatinine sulfate, cocaine, dibenamine and yohimbine as the hydrochloride, and mepyramine as the maleate.

RESULTS

Comparison of effects of intravenous injections of starch, clot, emboli, and serotonin on the systemic arterial blood pressure. Six cats were used for these experiments. Starch emboli caused either no effects or a transient profound fall in blood pressure associated with missed heart beats and further cardiac irregularities; this pattern of events was often repeated within 1 or 2 minutes.

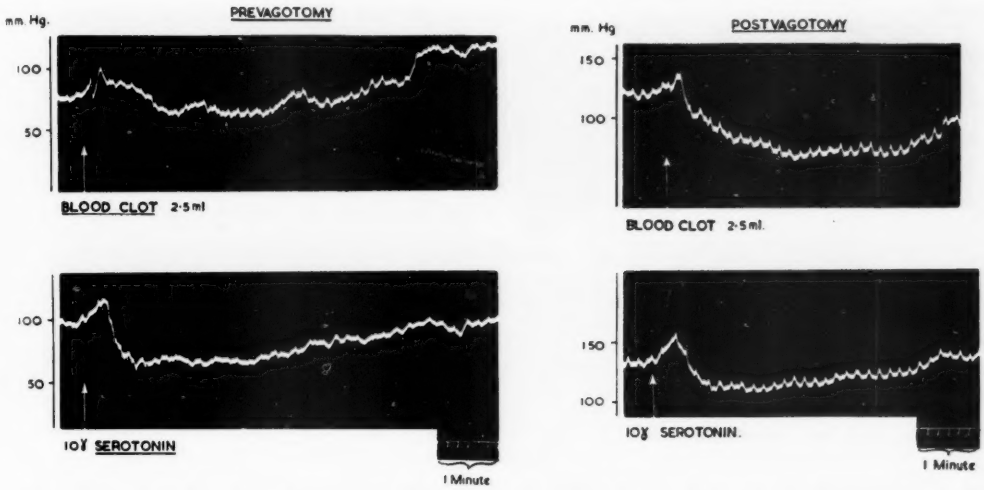

FIG. 2. The effect of a 2.5 milliliter normal saline suspension of cat's own blood clot and of 10 gammas of serotonin before and after the performance of cervical vagotomy.

In contrast, the effect of a blood clot embolism was a profound and steep fall in blood pressure, of some considerable duration; during the fall the cardiac pulsations often became feeble, and, on occasion, the float of the mercury manometer wrote a smooth line only on the smoked drum. When oscillations were still discernible there was marked cardiac slowing which was followed in turn by a period of compensatory hypertension and quickening of the rate. The latter findings were never seen with the starch emboli. The effects of the serotonin injection, however, closely paralleled those of the fragmented clot in all experiments (Fig. 1).

Nature of the blood pressure response to blood clot emboli serotonin. Evidence will be presented that the fall in blood pressure may be the result of three components; only the first has been systematically analyzed. (a) obstruction in the pulmonary circulation; (b) reflex slowing of the heart, with reduction in cardiac output; (c) vasodilatation.

In 2 experiments it was found that bilateral cervical vagotomy did not abolish the depressor effect of blood clot or serotonin (Fig. 2). The effect is therefore unlikely to be the result of cardiac slowing alone.

In 4 experiments direct peripheral vasodilatation followed the injection of 2 milliliters of blood clot suspension and serotonin, particularly elicited by injecting both substances into the pulmonary vein so that they circulated to many other tissues before reaching the lungs (Fig. 3, *3* and *4*). This effect was not always observed: in 2 other animals the direct vasoconstrictor properties of serotonin or of blood clot appeared to predominate (Fig. 3, *1* and *2*). The peripheral vasodilator effect when present may itself be reflex and the result of vasoconstriction at the other sites but this has not been further analyzed. Evidence is presented below to show that the main effect of serotonin and blood clot in producing hypotension is by obstructing the pulmonary circulation; the fall in blood pressure produced is not abolished by vagotomy, transection of the spinal cord at the cervical level, or by carotid sinus denervation. Humoral effects due to acetylcholine and histamine were excluded by the use of selective antagonists; atropine, 1 milligram per kilogram, did not prevent the depressor activity of blood clot or of serotonin. Mepyramine maleate (1 mgm./kgm.) influenced the fall in blood

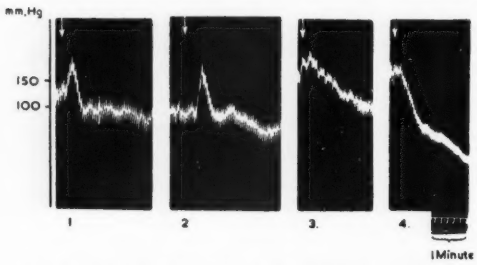

FIG. 3. An injection into the pulmonary vein of 5 gammas of serotonin (*1* and *3*) and of 2 milliliter blood clot suspension (*2* and *4*) was made. This usually results, both with serotonin and blood clot, in a rise of the systemic arterial pressure as shown in *1* and *2*. Occasionally a depressor response is given as in *3* and *4*.

pressure only slightly or in other cases produced no significant change (Fig. 4). Histamine is known to be released in fair amounts in clotting blood. Our findings at this stage would tend to indicate that histamine or its release from the tissues had little significance as the causative factor of the vascular depression.

To show that the active principle in fragmented blood clot is similar to serotonin itself. In the analysis of the similarities between serotonin itself and those of blood clot use was made of agents which are known to potentiate or inhibit the effects of serotonin. The experiments were carried out on 2 animals in each group.

a. Dibenamine (20 mgm./kgm.) antagonized the vascular effects of serotonin, serum, and blood clot; little activity was shown by the plasma samples before or after dibenamine (Fig. 5).

b. Similar results were obtained with the yohimbine salt (2 mgm./kgm.) as a serotonin antagonist (Fig. 6).

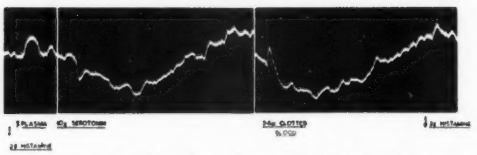

FIG. 4. Administration of an antihistamine (mepyramine maleate) does not alter the depressor effect of either serotonin or blood clot suspension on the arterial systemic blood pressure. Serotonin and blood clot were injected into the femoral vein.

c. Cocaine (8 mgm./kgm.) potentiated the vascular effects of serotonin blood clot and serum (Fig. 7).

d. Five hundred milligrams of 2-ethyl: 3-nitroindole, an antimetabolite of serotonin, was fed every 8 hours over 48 hours to cats and the effect of this treatment with a serotonin antimetabolite on the blood pressure response to serotonin and blood clot observed. Following the administration of serotonin and of blood clot there was little change of arterial blood pressure (Fig. 8).

Reviewing these results, the active substance in fragmented blood clot causing the vasodepressor response was influenced in all cases in the same manner as serotonin itself and therefore must be allied to, or even identical with it. From the blood pressure responses it would appear that the greatest amount of the active substance is present in clotted blood. It is present also in high concentration in serum and scarcely or not at all in plasma from centrifuged heparinized blood especially when care has been taken to prevent platelet disruption.

Assuming that the serotonin-like substance present in serum and blood clot, but absent almost entirely from the plasma, might be associated, as is serotonin, with the platelets of the blood, an experiment was performed injecting lysed cells of the buffy layer of a 2 milliliter sample of centrifuged, heparinized blood. The depressor effects of the lysed buffy layer greatly exceeded that of serum and of blood clot (Fig. 9).

Estimation by biologic assay of the amounts of serotonin in plasma, serum, and blood clot. The amounts of serotonin present in extracts of plasma, serum, and blood were estimated by biologic assay in 14 animals and a typical result using guinea pigs' ileum preparation (treated as described under "Methods") was as follows: serum, 4.3 micrograms per milliliter; clot, 6.2 micrograms per milliliter; whole blood (heparinized), 1.8 micrograms per milliliter. The serotonin present in clotted and heparinized blood samples was also estimated in 12 experiments done by the rat colon method. The relative po-

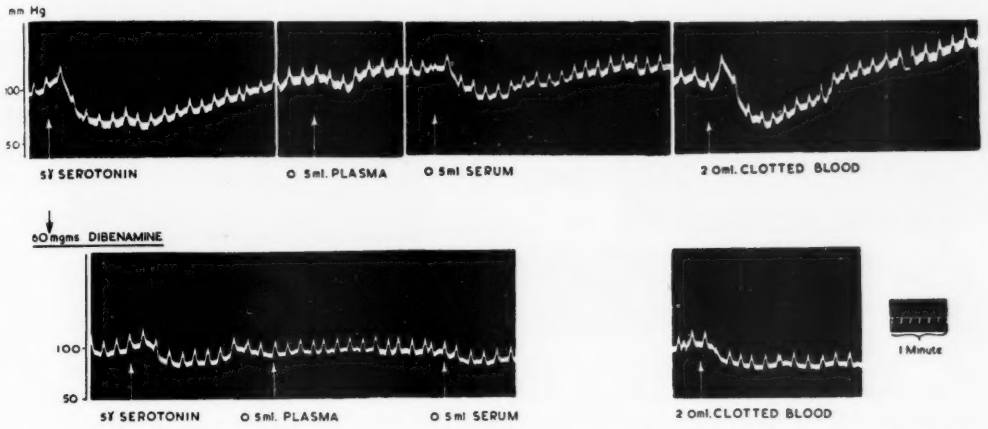

FIG. 5. The systemic arterial blood pressure responses to the intravenous injection of both serotonin and blood clot are greatly diminished after the administration of dibenamine.

tencies of the samples of plasma, serum, lysed buffy layer taken from the heparinized sample and of blood clot were as follows: plasma, 1; lysed buffy layer, 104; whole blood (heparinized: nonextracted), 28; whole blood (extracted), 108; serum, 45; clot, 80. By far the greatest amount of serotonin is to be found in the lysed buffy layer and, least of all, in the plasma; serum and blood clot contain considerable amounts of serotonin.

The site of action of the humoral substance. In several experiments biphasic responses in the blood pressure were met, and it was frequently observed that as a result of changes in the level of anesthesia following administration of chloralose, primary pressor responses could be produced.

While there is little doubt that a main effect of serotonin is direct vasoconstriction this substance is capable of producing very large falls in blood pressure, especially in our experience, when small doses only are administered; that this is related to the action of serotonin in the lung bed, and in the case of blood clot to a similar action in this area, may be demonstrated directly as follows:

The injection of 5 micrograms per kilogram of serotonin and 2.5 milliliters of blood clot into the jugular vein or into the right auricle of a cat with the thorax open pro-

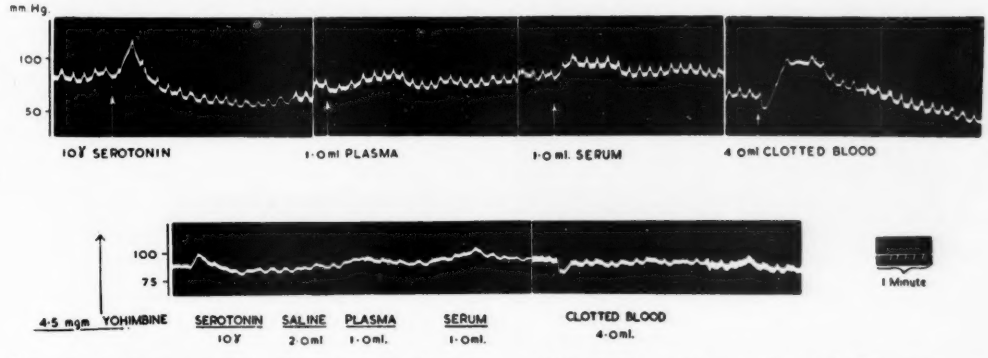

FIG. 6. As demonstrated in Figure 5, after the administration of yohimbine, the effect of both serotonin and blood clot on the systemic arterial blood pressure is diminished.

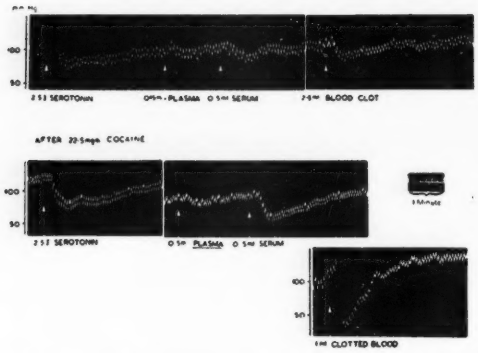

FIG. 7. After administration of cocaine the arterial systemic response to intravenous injection of serotonin and blood clot is augmented.

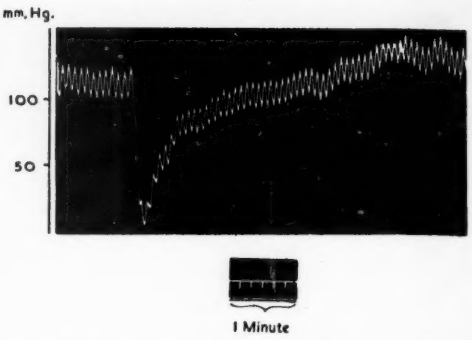

FIG. 9. The effect on systemic arterial pressure of injecting into femoral vein, lysed buffy layer of cells from 2 milliliters of animal's own blood after centrifugation.

duces swelling of the pulmonary artery and of the right side of the heart, and the pulmonary arterial pressure rises steeply to 48 to 80 millimeters of mercury. The pressure in the carotid artery starts to fall shortly after the beginning of the rise in the pulmonary artery; within 1 to 2 seconds fall in peripheral blood pressure is at a maximum and cardiac embarrassment is indicated by the fact that the pulse pressure as read from the carotid pressure tracing is very low (Fig. 10).

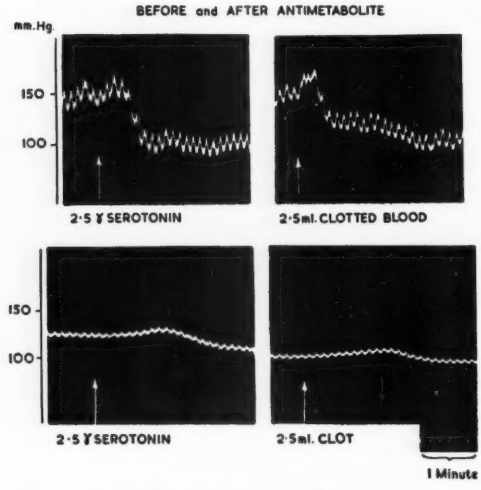

FIG. 8. The diminution in response of the arterial systemic blood pressure to both serotonin and blood clot after feeding the cat for 48 hours on an antimetabolite of serotonin (2-ethyl: 3-nitroindole) is shown.

Repeated injection leads to tachyphylaxis. All these effects are at a maximum in the vagotomized or atropinized animal, since in these ways slowing of the heart has been eliminated. The effects are minimal when the injection is made into the left auricle, thereby allowing systemic circulation to occur before the lung is reached.

Both serotonin and blood clot, which by taking measurements of the pressures in the pulmonary arterial bed can be shown to give rise to pulmonary hypertension, no longer give this effect after the administration of serotonin antimetabolite or antagonist, e.g., dibenamine (Fig. 11).

Antagonism with heparin and other substances. It is well known from clinical experience that heparin exerts a beneficial effect on the outcome of pulmonary embolism. It is believed that this is brought about by preventing further thrombosis, by lessening the risk of embolization from the site of primary detachment of the clot and by activation of proteolytic ferments which lessen the size of the embolus. In several experiments we have been able to demonstrate a degree of antagonism between serotonin and heparin which leads us to believe that heparin may exert a further beneficial effect through neutralization of the serotonin present in the clot itself or that coming from the infarcted area. We have observed that serotonin injected into the heparinized animal loses its vascular

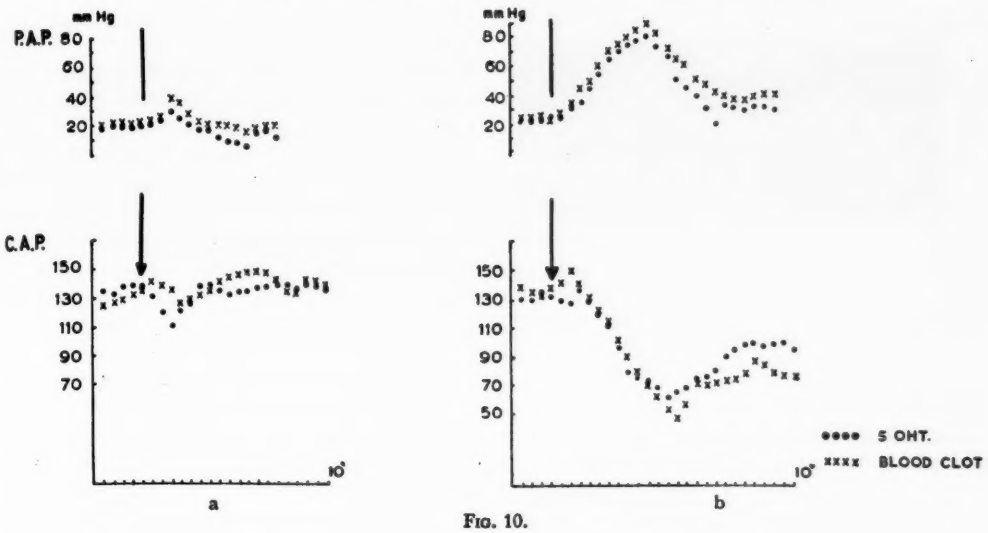

FIG. 10.

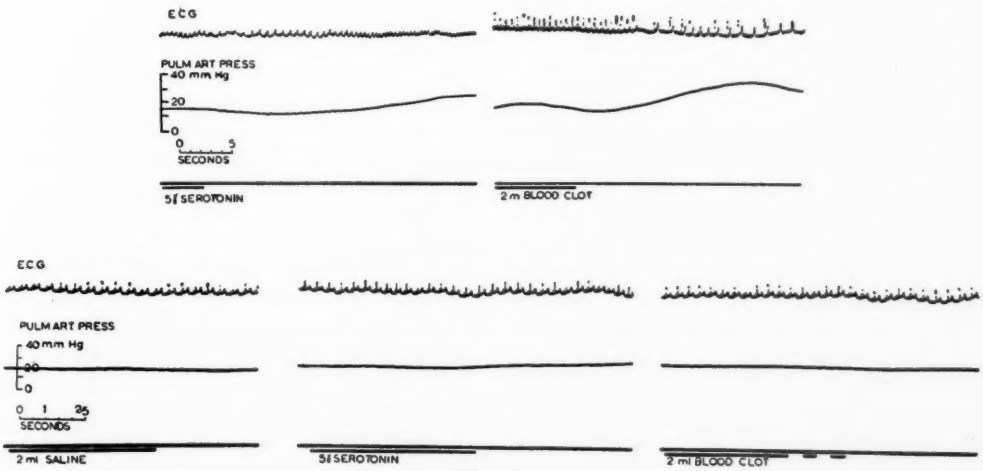

FIG. 11.

FIG. 10. Blood clot and serotonin were injected separately into: a, the left auricle and, b, the external jugular vein, at the points indicated by the arrows. When injected into the left auricle, the alterations in the pulmonary arterial pressure (P.A.P.) and the systemic arterial pressure (C.A.P.) were minimal when compared with the changes when the injection is made into the external jugular vein. Time along the horizontal axis in seconds; 2.5 milliliters of blood clot suspension and 5 gammas of serotonin (OHT) were injected in each case.

FIG. 11. Simultaneous electrocardiogram and pulmonary arterial tracings to show that the effect of injection of blood clot and serotonin (upper trace) was abolished after feeding the animal for 48 hours with serotonin antimetabolite (2-ethyl: 3-nitroindole).

depressant effects (Fig. 12). In vitro titration of heparin against serotonin-induced activity of the rat colon preparation demonstrates this antagonism; after injection of ½ milligram of heparin into the bath the preparation becomes inactive and may remain so for 15 to 20 minutes before the former contractile activity to serotonin is regained (Fig. 13).

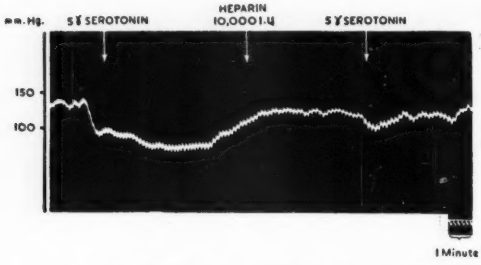

FIG. 12. The effect of 5 gammas of serotonin intravenously, on the systemic arterial blood pressure before and after heparinization of the animal.

DISCUSSION

Serotonin has been found in considerable quantities in platelets and clotted-blood serum. An injection of an antiplatelet serum can produce profound circulatory depression and this method has been extensively used in the study of experimental shock. This substance has high biologic activity as is seen in the present experiments in which 2 micrograms per kilogram of body weight produced changes in the cat's systemic blood pressure. Further, we believe that the experiments described indicate that there are appreciable amounts of serotonin in the clotted blood injected into the animal to produce pulmonary emboli. We believe that this humoral factor increases the mechanical blockage and the vasodepressor reflexes arising therefrom in a case of pulmonary embolism. Moreover, the presence of such a humoral substance would help to explain the symptoms, sometimes severe, which may occur when a pulmonary embolus is quite small, or when (as is fairly common) pulmonary thrombosis is the predominating pathologic feature.

It is almost certain that the effects described are not entirely mediated by the action of serotonin. We have not excluded, for instance, the possibility that the depression of the vascular system (which resembles closely that described by Emmelin and Feldberg as occurring after injections of adenosine triphosphate) is contributed to by this substance exerting its effects by releasing serotonin or vice versa. In a similar way, although the effects described for blood clot injected into the circulation are barely contributed to by histamine present in clot and serum, we have not excluded other effects due to release of histamine indirectly from the tissues themselves by 5-hydroxytryptamine in clot and serum acting as a histamine releasing agent. It has been shown by Feldberg and Smith that serotonin has in common with other amines this property; local release of histamine and heparin, located together in lung mast cells, would readily contribute to the general shock and also to the tendency to local hemorrhage into the lung infarcts.

One justifiable criticism of the method used in these experiments is that the clot injected is relatively fresh and might therefore be expected to contain high concentrations of serotonin; in clinical cases the clot forming the embolus may be older. In such cases, however, it is likely that subsequent on the impaction of the clot in the lung vessel there may be breakdown of blood cells and infarction of the lung tissue, subtended by the plugged arterial branch, with release of sero-

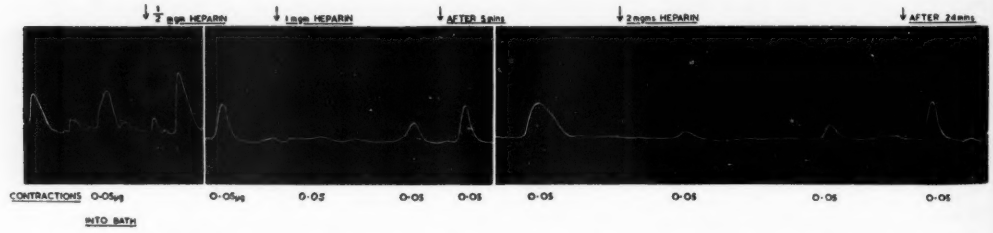

FIG. 13. The antagonistic effect of heparin to serotonin on the rat colon preparation. Note the inhibition of colon contractions to serotonin caused by adding varying amounts of heparin to the organ bath.

tonin from this area. In the type of case described by Dew in 1953 in which clotting occurs spontaneously in the lung vessels giving rise to symptoms similar to those of pulmonary embolism the production of relatively large amounts of serotonin is even more likely, and no doubt contribute to the patient's symptoms.

It must also be borne in mind as we have shown that the effect of serotonin in producing circulatory collapse is maximal when this substance is introduced directly into the pulmonary vascular bed. Thus both the liberation of serotonin from the clot and the infarcted tissue is taking place at the site calculated to elicit the most active circulatory changes.

While it is dangerous to apply directly results obtained in experimental animals, there are several therapeutic implications in the results obtained so far. We have confirmed that serotonin is liberated from the platelets and is present in blood clot. If the platelets are protected from disruption by heparin the effects of embolization are less marked—a fact well known clinically. Besides protecting against platelet disruption, however, heparin has now been shown to have a direct neutralizing effect against serotonin.

Therapeutic applications of serotonin inhibitors and antiserotonin metabolites should also be explored, yet so far as we are aware they have no effect on the clotting process. There is the disadvantage that after administration of the antimetabolite orally, a latent period of 12 to 48 hours is required for the effective agent to have been synthesized in the body in the concentrations required to exert a competitive effect; such a delay would never be permissible when confronted with this emergency.

SUMMARY

1. Serotonin and blood clot produce a fall in blood pressure which is not abolished by vagotomy or antihistamine drugs; it is potentiated by cocaine and is minimized by dibenamine, yohimbine, and treatment with 2-ethyl: 3-methyl: 5-nitroindole, known serotonin antagonists.

2. Serotonin is released into the serum of clotting blood and is present in the blood clot itself. It is present in highest concentration in the buffy layer of centrifuged, heparinized blood; lysed platelets from the buffy layer are seen to produce a marked vascular depression.

3. Serotonin and blood clot both cause, on systemic injection, a rise in the pulmonary arterial pressure. When injected so as to by-pass the lung bed the vascular effects are minimized.

4. An antagonism between heparin and serotonin has been demonstrated in vivo and in vitro.

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RESPIRATORY HAZARDS OF OPIATES AND OTHER NARCOTIC ANALGESICS

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DURING THE COURSE of an investigation into the effect of anesthetic agents upon the development of respiratory acidosis, a large volume of data pertaining to opiate and opiate-like drugs has been accumulated (1). Many of these data have clinical implications which underline the potency and hazards of narcotic analgesics. This report has been written to emphasize such pitfalls. They will be demonstrated by data and discussion dealing with the prolonged effect of commonly employed narcotics upon respiratory rate, minute and tidal volume, "alveolar" carbon dioxide pressure (pCO_2), and response to endogenously accumulated carbon dioxide.

METHODS

The methods employed have been described in detail elsewhere (2). In brief, a closed circuit system incorporating a 6 liter spirometer, an infra-red carbon dioxide analyzer, and carbon dioxide absorption canisters which can be shunted out of the system has been used. Unidirectional flow of respired gases was produced by respiratory valves attached to a mouthpiece. Continuous respiratory tracings were obtained. End expiratory carbon dioxide concentrations were recorded on an oscillograph. Arterial blood pressure was recorded with a capacitance manometer, and continuous electrocardiographic tracings were obtained.

Control observations of respiration were made in 24 normal subjects or patients scheduled for elective operations. The response to endogenously accumulated carbon dioxide was then measured, according to the method described by Loewy and modified by us (2, 3). Following a return to normal, morphine sulfate (10 to 15 mgm.), meperidine hydrochloride (demerol) (100 to 125 mgm.), codeine sulfate (60 mgm.), alphaprodine (nisentil) (40 to 60 mgm.), dihydromorphinone hydrochloride (dilaudid) (2 to 3 mgm.), methadone hydrochloride (7.5 to 8.0 mgm.), or secobarbital sodium (seconal) (100 to 150 mgm.) was injected intramuscularly. Therapeutic dosage was attempted in each instance. Repeat observations were then made at 30 minutes, 1 hour, and at hourly intervals thereafter.

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Dr. Helrich is a Postdoctorate Fellow of the National Heart Institute.

RESULTS

The data from 3 control responses to endogenously accumulated carbon dioxide in the same subject are shown in Table I. The figures indicate a reasonably reproducible test. It is of note that the control pCO_2 of subject J. M. was 52 millimeters of mercury. This is higher than any control observation in all other subjects, the average of which was 44 ± 3.7 millimeters of mercury. Subject J. M. was observed 3 times over a period of 6 weeks. On 2 occasions his pCO_2 was 52 and on the third 44. We could uncover no reason for the high reading.

Observations from 4 subjects or patients to whom morphine was administered are tabulated in Table II. In 1 subject there was a slight increase in respiratory rate following injection of the opiate, although the minute volume had diminished 25 per cent. In 3 subjects no marked change in respira-

TABLE I.—RESPONSE TO CO_2

		Control 1		Control 2 (45 Min.)		Control 3 (1 Hr., 30 min.)	
		Control	CO_2*	Control	CO_2*	Control	CO_2*
J.M., male	End exp. pCO_2 (mm. Hg)	53	74	53	74	52	74
Age, 32 yrs.	Resp. rate/min.	11	17	11	14	11	13
Wt., 185 lbs.	Tidal vol. (c.c.)	500	2600	500	2550	500	3400
Ht., 73″	Min. vol. (L./min.)	5.5	44	5.5	36	5.5	44

*Throughout the tables the column headed CO_2 indicates the response to endogenously accumulated carbon dioxide (rebreathing).

TABLE II.—RESPONSE TO MORPHINE SULFATE

		Time after administration: Control		30 Minutes		1 Hour		2 Hours		3 Hours		4 Hours	
		Control	CO_2	Control	CO_2	Control	CO_2	Control	CO_2	Control	CO_2	Control	CO_2
W.B., male, 24 yrs.	End exp. pCO_2	48	67	51	69	52	67	52	67	51	67	51	68
Ht. 67″, wt. 179 lbs.	(mm. Hg)												
Morphine 15 mgm.	Resp. rate/min.	11	16	12	14	11	13	11	14	11	13	10	13
0.2 mgm./kgm.	Tidal vol. (c.c.)	550	2225	400	1475	450	1050	400	900	400	950	450	1125
	Min.vol.(L./min.)	6.1	35	4.8	21	5.0	14	4.4	13	4.4	12	4.5	15
J.M., male, 32 yrs.	End exp. pCO_2	52	72	53	72	54	72	57	73	54	73	56	75
Ht. 73″, wt. 185 lbs.	(mm. Hg)												
Morphine 15 mgm.	Resp. rate/min.	11	17	10	12	12	13	10	13	11	14	11	14
0.18 mgm./kgm.	Tidal vol. (c.c.)	530	2600	510	1975	425	2200	380	1200	400	1150	400	1350
	Min.vol.(L./min.)	5.7	44	5.0	24	5.0	29	3.8	16	4.4	16	4.4	20
W.M., male, 62 yrs.	End exp. pCO_2	43	70	46	70	45	71	—	—	—	—	—	—
Ht. 70″, wt., 165 lbs.	(mm. Hg)												
Morphine 10 mgm.	Resp. rate/min.	12	15	14	14	13	20	—	—	—	—	—	—
0.13 mgm./kgm.	Tidal vol. (c.c.)	400	1500	310	1600	300	1280	—	—	—	—	—	—
	Min.vol.(L./min.)	4.8	23	4.3	22	3.9	26	—	—	—	—	—	—
C.S., male, 50 yrs.	End exp. pCO_2	40	63	44	64	40	63	—	—	—	—	—	—
Ht. 70″, wt. 188 lbs.	(mm. Hg)												
Morphine 10 mgm.	Resp. rate/min.	15	20	13	21	17	21	—	—	—	—	—	—
0.11 mgm./kgm.	Tidal vol. (c.c.)	330	1620	330	1060	325	1160	—	—	—	—	—	—
	Min.vol.(L./min.)	4.9	32	4.3	22	5.5	27	—	—	—	—	—	—

tory rate was observed, yet the minute volume was reduced an average of 22 per cent. Three of the 4 subjects or patients demonstrated a markedly diminished respiratory response to the carbon dioxide stimulus after opiate administration. In the 2 individuals whose respiratory rate remained unchanged after morphine, the respiratory response to carbon dioxide was reduced 66 per cent in 1 and slightly increased in the other. In 2 subjects maximal respiratory depression was not reached until 3 hours after the drug was injected and was only slightly less than maximal at 4 hours. Two subjects had unpleasant side effects of morphine (nausea, anorexia, lethargy, vertigo, dysphoria) for 20 hours after the drug had been administered.

The data from 3 subjects to whom dihydromorphinone was administered are summarized in Table III. Two of the subjects demonstrated an increased respiratory rate and the third had only a transient depression followed by a more rapid respiration. The minute volume was decreased in all 3, although only temporarily in 1. After the opiate the respiratory response to the carbon dioxide stimulus was reduced 41 per cent in 2 patients and 49 per cent in the third. Unpleasant side effects were less pronounced with dihydromorphinone, lasting 5, 3, and 3 hours respectively.

Table IV summarizes observations from 4 subjects or patients to whom meperidine was administered. In 1, the respiratory rate increased; in 2 the change was slight; and in the fourth the rate decreased. The minute volume was diminished in all 4, with an average of 21 per cent. Significant reductions in the response of minute volume to the carbon dioxide stimulus were apparent in all individuals with an average reduction of 48 per cent. Subject F. H., whose respiratory rate increased following meperidine, demonstrated a response of only 37 per cent

TABLE III.—RESPONSE TO DIHYDROMORPHINONE HYDROCHLORIDE (DILAUDID)

		Time after administration											
		Control		*30 Minutes*		*1 Hour*		*2 Hours*		*4 Hours*		*5 Hours*	
		Control	*CO_2*	*Control*	*CO_2*	*Control*	*CO_2*	*Control*	*CO_2*	*Control*	*CO_2*	*Control*	*CO_2*
K.K., male, 36 yrs.	End exp. pCO_2	45	64	50	63	48	63	48	67	—	—	—	—
Ht. 68″, wt. 148 lbs.	(mm. Hg)												
Dihydromorphinone	Resp. rate/min.	13	14	13	14	14	14	13	14	—	—	—	—
(2 mgm.)	Tidal vol. (c.c.)	430	1250	360	875	330	750	370	975	—	—	—	—
0.03 mgm./kgm.	Min. vol. (L./min.)	5.6	17.5	4.7	12.2	4.6	10.3	4.8	13.6	—	—	—	—
G.S., male, 24 yrs.	End exp. pCO_2	42	55	40	55	42	56	44	55	—	—	—	—
Ht. 68″, wt. 135 lbs.	(mm. Hg)												
Dihydromorphinone	Resp. rate/min.	8	12	7	10	14	12	15	11	—	—	—	—
(2 mgm.)	Tidal vol. (c.c.)	660	1650	730	1250	390	850	380	1225	—	—	—	—
0.032 mgm./kgm.	Min. vol. (L./min.)	5.3	20	5.1	12.5	5.5	10.2	5.7	13.4	—	—	—	—
N.B., male, 25 yrs.	End exp. pCO_2	46	66	50	66	47	65	*48	66	50	66	50	67
Ht. 70″, wt. 195 lbs.	(mm. Hg)												
Dihydromorphinone	Resp. rate/min.	13	12	15	9	17	7	16	13	16	11	14	9
(3 mgm.)	Tidal vol. (c.c.)	550	2400	360	2125	400	3150	420	1300	350	1550	500	2350
0.33 mgm./kgm.	Min. vol. (L./min.)	7.2	29	5.5	19	7.0	22	6.7	17	5.6	17	7.1	21

*3 hours.

TABLE IV.—RESPONSE TO MEPERIDINE HYDROCHLORIDE (DEMEROL)

		Time after administration											
		Control		*30 Minutes*		*1 Hour*		*2 Hours*		*3 Hours*		*4 Hours*	
		Control	*CO_2*	*Control*	*CO_2*	*Control*	*CO_2*	*Control*	*CO_2*	*Control*	*CO_2*	*Control*	*CO_2*
F.H., male, 26 yrs.	End exp. pCO_2	40	65	50	65	49	63	48	65	49	68	53	67
Ht. 70″, wt., 145 lbs.	(mm. Hg)												
Meperidine 125 mgm.	Resp. rate/min.	9	15	11	20	11	16	12	17	13	15	14	15
1.42 mgm./kgm.	Tidal vol. (c.c.)	630	2325	400	875	440	1000	390	1025	425	950	420	825
	Min. vol. (L./min.)	5.7	35	4.4	17.5	4.8	16.0	4.7	17.8	5.5	14.2	5.9	12.4
M.S., male, 28 yrs.	End exp. pCO_2	40	64	41	60	45	61	39	61	40	61	**38	**63
Ht. 68″, wt. 134 lbs.	(mm. Hg)												
Meperidine 100 mgm.	Resp. rate/min.	6	18	6	15	5	16	5	11	5	13	7	14
1.64 mgm./kgm.	Tidal vol. (c.c.)	700	1950	675	1300	700	1250	900	1575	1050	1300	770	1550
	Min. vol. (L./min.)	4.2	35.1	4.1	19.5	3.5	20.0	4.9	17.3	6.0	16.9	5.6	21.7
W.H., male, 69 yrs.	End exp. pCO_2	44	70	44	70	*44	*70	47	71	50	72	—	—
Ht. 66″, wt. 159 lbs.	(mm. Hg)												
Meperidine 60 mgm.	Resp. rate/min.	20	23	19	20	18	19	19	19	18	18	—	—
0.86 mgm./kgm.	Tidal vol. (c.c.)	285	910	250	600	310	940	270	560	255	880	—	—
	Min. vol. (L./min.)	5.7	21.7	4.8	12.0	5.6	17.9	5.1	11.1	4.6	15.8	—	—
R.D., male, 62 yrs.	End exp. pCO_2	35	72	42	63	*34	*63	38	63	38	65	—	—
Ht. 70″, wt. 158 lbs.	(mm. Hg)												
Meperidine 75 mgm.	Resp. rate/min.	14	14	11	11	10	12	11	13	11	12	—	—
1.04 mgm./kgm.	Tidal vol. (c.c.)	430	1375	370	1400	520	1450	545	1100	380	1275	—	—
	Min. vol. (L./min.)	6.0	19.9	4.1	15.4	5.2	17.4	6.0	14.3	4.2	5.3	—	—

*Surgical anesthesia established with cyclopropane in the case of W.H. and spinal to D-4 in the case of R.D.
**5 hours.

of normal to the carbon dioxide stimulus 4 hours after administration of the drug, while the response of subject M. S. was 62 per cent of normal 5 hours after the opiate. Side effects of meperidine were apparent for 5 hours in 2 subjects.

Table V contains data from 2 subjects given methadone. Respiratory rate was not decreased, but diminution in tidal and minute volume occurred in both. Reduced response to the carbon dioxide stimulus was apparent at 4 hours in both subjects and was still evident at 5 hours in 1 subject. Unpleasant side effects were persistent for 6 to 7 hours.

Observations were made in 3 subjects to whom alphaprodine was administered (Table VI). Depression in respiratory rate was apparent in 2 of the 3. Reduction in minute volume was obvious in all 4, with or without the carbon dioxide stimulus. Unpleasant side effects lasted 10, 10, and 5 hours.

Observations upon 2 subjects receiving codeine are recorded in Table VII. Respiratory rate was not reduced in either subject. Both displayed an elevated pCO_2, and depression in tidal and minute volume. The response to the carbon dioxide stimulus was diminished for 2 hours in 1 subject. Side

TABLE V.—RESPONSE TO METHADONE HYDROCHLORIDE

		Time after administration											
		Control		*30 Minutes*		*1 Hour*		*2 Hours*		*4 Hours*		*5 Hours*	
		Control	CO_2	*Control*	CO_2	*Control*	CO_2	*Control*	CO_2	*Control*	CO_2	*Control*	CO_2
F.H., male, 26 yrs.	End exp. pCO_2	44	71	50	71	48	71	50	71	50	73	53	72
Ht. 71″, wt. 192 lbs.	(mm. Hg)												
Methadone (8 mgm.)	Resp. rate/min.	12	18	11	18	11	15	12	16	13	17	12	19
0.09 mgm./kgm.	Tidal vol. (c.c.)	450	2200	325	1575	340	1425	370	1425	350	2100	380	2275
	Min. vol. (L./min.)	5.0	40	3.5	28	3.9	21	4.3	23	4.5	36	4.5	43
M.B., male, 21 yrs.	End exp. pCO_2	45	70	49	68	50	71	52	70	*49	*70	**48	**72
Ht. 72″, wt. 180 lbs.	(mm. Hg)												
Methadone (7.5 mgm.)	Resp. rate/min.	9	12	10	12	8	13	11	13	11	13	11	14
0.09 mgm./kgm.	Tidal vol. (c.c.)	560	2125	475	1350	560	1475	400	1375	400	1700	425	1425
	Min. vol. (L./min.)	5.0	26	5.0	16	4.6	19	4.2	18	4.3	22	4.9	20

*3½ hours.
**4½ hours.

TABLE VI.—RESPONSE TO ALPHAPRODINE (NISENTIL)

		Time after administration									
		Control		*30 Minutes*		*1 Hour*		*2 Hours*		*3 Hours*	
		Control	CO_2	*Control*	CO_2	*Control*	CO_2	*Control*	CO_2	*Control*	CO_2
R.S., male, 24 yrs.	End exp. pCO_2 (mm. Hg)	48	74	52	74	51	74	50	74	49	75
Ht. 70½″, wt. 180 lbs.	Resp. rate/min.	13	18	12	16	14	19	13	17	14	19
Alphaprodine 45 mgm.	Tidal vol. (c.c.)	460	2650	410	1500	400	1475	375	2000	315	1850
0.55 mgm./kgm.	Min. vol. (L./min.)	6.1	37	5.0	26	5.4	28	4.9	34	4.4	35
W.S., male, 27 yrs.	End exp. pCO_2 (mm. Hg)	36	55	49	58	43	58	—	—	—	—
Ht. 68″, wt. 145 lbs.	Resp. rate/min.	13	14	11	11	9	20	—	—	—	—
Alphaprodine 60 mgm.	Tidal vol. (c.c.)	500	1825	460	1200	490	1000	—	—	—	—
0.90 mgm./kgm.	Min. vol. (L./min.)	6.5	26	5.1	13	4.4	20	—	—	—	—
D.D., male, 28 yrs.	End exp. pCO_2 (mm. Hg)	44	65	51	69	48	64	43	63	*44	*65
Ht. 71″, wt. 165 lbs.	Resp. rate/min.	12	17	10	14	13	16	11	14	12	13
Alphaprodine 60 mgm.	Tidal vol. (c.c.)	440	1625	400	850	390	875	450	1400	400	1650
0.80 mgm./kgm.	Min. vol. (L./min.)	5.3	28	4.0	12	5.1	14	5.0	20	4.8	21

*2½ hours.

effects were not pronounced in either subject.

Data pertaining to the effects of dromoran have recently been published (3), and are reproduced here for completeness of presentation (Table VIII). In 3 subjects, respiratory rate was diminished in 2 and unchanged in 1. Respiratory tidal volume was elevated in one and essentially unchanged in the other. Minute volume was reduced in 1 and relatively unchanged in 2. The respiratory response to endogenously accumulated carbon dioxide was reduced markedly in all 3.

For comparison, the data from 3 subjects to whom secobarbital sodium was administered are presented in Table IX. There was an increase in respiratory rate in 1 subject, a decrease in rate in 1, and no change in the third. There was a diminution of minute volume in 1 subject and no essential change in the other 2. The pCO_2 was not significantly altered in any of the 3 subjects. A transitory depression in respiratory response to carbon dioxide was observed in 1 subject and no diminution was seen in the other 2 subjects. The drug produced sleep in all 3 subjects.

DISCUSSION

There are several ways of determining the presence of respiratory depression. The obvious ones are: (a) record respiratory rate; (b) measure respiratory tidal volume; (c) then calculate respiratory minute volume; and, (d) determine "alveolar" or arterial pO_2 or pCO_2. A less obvious method is to test the response of the respiratory center to increased concentrations of carbon dioxide.

The latter test is not new. Loewy employed carbon dioxide in this manner in 1890. Since that time, variations of the test have been employed by Schmidt and Harer and by Loeschcke and associates. Our method differs only in that it employs endogenously accumulated carbon dioxide.

TABLE VII.—RESPONSE TO CODEINE SULFATE

		Time after administration									
		Control		30 Minutes		1 Hour		2 Hours		3 Hours	
		Control	CO_2	Control	CO_2	Control	CO_2	Control	CO_2	Control	CO_2
J.C., male, 26 yrs.	End. exp. pCO_2 (mm. Hg)	42	66	41	66	45	65	46	66	46	66
Ht. 69″, wt. 155 lbs.	Resp. rate/min.	13	14	15	15	15	15	14	13	15	13
Codeine 60 mgm.	Tidal vol. (c.c.)	460	3100	320	2100	400	1550	400	1900	400	3150
0.85 mgm./kgm.	Min. vol. (L./min.)	5.8	42	4.5	32	6.0	23	5.7	25	5.8	41
C.R., male, 23 yrs.	End exp. pCO_2 (mm. Hg)	43	71	46	72	48	72	—	—	—	—
Ht. 73″, wt. 175 lbs.	Resp. rate/min.	15	16	15	15	15	14	—	—	—	—
Codeine 60 mgm.	Tidal vol. (c.c.)	375	1900	300	1750	300	2400	—	—	—	—
0.75 mgm./kgm.	Min. vol. (L./min.)	5.6	31	4.5	26	4.5	34	—	—	—	—

TABLE VIII.*—RESPONSE TO DROMORAN HYDROBROMIDE

		Time after administration									
		Control		30 Minutes		1 Hour		2 Hours		3 Hours	
		Control	CO_2	Control	CO_2	Control	CO_2	Control	CO_2	Control	CO_2
J.M., male, 21 yrs.	End exp. pCO_2 (mm. Hg)	44	69	53	70	53	73	55	74	—	—
Ht. 72″, wt. 170 lbs.	Resp. rate/min.	10	14	9	10	8	11	10	11	—	—
Dromoran HBr. (7.5 mgm.)	Tidal vol. (c.c.)	550	2500	675	1800	650	1925	575	2225	—	—
0.097 mgm./kgm.	Min. vol. (L./min.)	5.5	35	6.1	18	5.2	21.2	5.8	24.5	—	—
R.G., male, 21 yrs.	End exp. pCO_2 (mm. Hg)	48	71	51	71	53	71	53	69	54	72
Ht. 70″, wt. 160 lbs.	Resp. rate/min.	14	15	11	13	10	13	10	12	10	14
Dromoran HBr. (7.0 mgm.)	Tidal vol. (c.c.)	500	1925	475	1525	525	1350	500	1300	550	1550
0.096 mgm./kgm.	Min. vol. (L./min.)	7.0	29.0	5.2	20.0	5.3	17.5	5.0	15.6	5.5	21.7
R.J., male, 32 yrs.	End exp. pCO_2 (mm. Hg)	45	66	47	62	46	65	49	69	—	—
Ht. 68″, wt. 148 lbs.	Resp. rate/min.	8	13	8	10	8	11	8	9	—	—
Dromoran HBr. (5.0 mgm.)	Tidal vol. (c.c.)	500	1800	550	1450	500	1600	500	1550	—	—
0.07 mgm./kgm.	Min. vol. (L./min.)	4.0	23.4	4.4	14.5	4.0	17.6	4.0	14.0	—	—

*Reproduced in part by permission of the *Journal of Pharmacology and Experimental Therapeutics* (3).

This implies that the stimulus is not steady but changes constantly because of the rising arterial carbon dioxide concentration. The effect, however, is readily reproducible in the same individual. The significance of the test lies in the fact that it subjects the patient to stress. Often the full effect of drugs is manifest only under stress. For instance, it is well established that morphine causes minimal nausea and vomiting if the patient remains supine but leads to a high incidence of the same if the patient assumes the erect position or becomes ambulatory. The effect of opiates upon the circulation is likewise often different if the patient is supine or erect. The present investigation has attempted to correlate evidences of respiratory depressant effect by opiates or opiate-like drugs by the use of all of these methods.

From the foregoing data certain characteristic respiratory effects of opiates are reemphasized. The first is that elevation of "alveolar" pCO_2 is an invariable accompaniment of opiate administration. In the 21 subjects to whom opiates or opiate-like drugs were given, all demonstrated a rise in pCO_2 with a range of 2 to 13 millimeters, an average elevation of 5.7 millimeters.

Subjects J. M. and R. J. (Table VIII) demonstrated a rise in pCO_2 while simultaneously increasing respiratory tidal volume and minute volume. The change in R. J. may not be significant since we have accepted $\pm$ 2 millimeters as being within the limits of error of our recording method. However, the rise in J. M. is definite. We have noted similar increases in other subjects and patients. In the absence of more complete pulmonary function measurements, especially dead space, any discussion of this finding would be mere speculation.

The second obvious effect of opiates was to decrease the respiratory minute volume. This was observed in 19 of the 21 subjects. The notable exceptions were the 2 subjects J. M. and R. J. mentioned previously, to whom dromoran had been administered. Respiratory tidal volume was definitely diminished in 15 of the 22 subjects with an

TABLE IX.—RESPONSE TO SECOBARBITAL SODIUM

		Time after administration							
		Control		*30 Minutes*		*1 Hour*		*2 Hours*	
		Control	*CO_2*	*Control*	*CO_2*	*Control*	*CO_2*	*Control*	*CO_2*
G.S., male, 24 yrs.	End exp. pCO_2 (mm. Hg)	48	62	48	63	46	64	—	—
Ht. 68″, wt. 140 lbs.	Resp. rate/min.	9	10	15	12	7	13	—	—
Secobarbital (200 mgm.)	Tidal vol. (c.c.)	540	2400	350	1600	700	2650	—	—
3 mgm./kgm.	Min. vol. (L./min.)	5.2	24	5.7	19	5.0	35	—	—
R.S., male, 24 yrs.	End exp. pCO_2 (mm. Hg)	46	73	46	70	46	72	46	72
Ht. 70½″, wt. 180 lbs.	Resp. rate/min.	13	16	13	18	13	19	13	18
Secobarbital (150 mgm.)	Tidal vol. (c.c.)	575	2325	475	2350	475	2250	500	200
2 mgm./kgm.	Min. vol. (L./min.)	7.5	37	6.2	42	6.2	43	6.5	36
D.D., male, 22 yrs.	End exp. pCO_2 (mm. Hg)	47	67	—	—	48	67	48	66
Ht. 67″, wt. 137 lbs.	Resp. rate/min.	16	16	—	—	14	19	13	19
Secobarbital (200 mgm.)	Tidal vol. (c.c.)	400	1350	—	—	450	1200	500	1325
3 mgm./kgm.	Min. vol. (L./min.)	6.4	21	—	—	6.3	23	6.5	26

equivocal change in 5 others. Subject J. M. again was the only one to demonstrate an increased tidal volume.

Respiratory rate was notably deficient as a guide to respiratory depression from the opiates. Only 6 of the 21 subjects demonstrated a diminished rate of breathing. Eleven had no change or an equivocal one and 4 developed a more rapid rate. It is apparent, therefore, that respiratory rate is not a reliable clinical guide for the administration of opiates to patients. Respiratory depression can exist without reduction in respiratory rate. Subject R. S. (Table VI) demonstrates this with a reduction of 28 per cent in minute volume and of 31 per cent in tidal volume despite a slight elevation in the respiratory rate.

The respiratory response to endogenously accumulated carbon dioxide was depressed after opiates or opiate-like drugs in all but 1 patient. This patient was studied for only 1 hour after morphine was administered (W.M. Table II). Usually this response continued to be diminished after other respiratory measurements returned to normal. Subjects W. B. and J. M. (Table II) demonstrated a diminished minute volume response of approximately 65 per cent 3 hours after morphine was administered and at 4 hours the response was still 56 per cent below normal. At this same time their unstimulated respiratory minute volume was approximately 25 per cent below the control level.

The respiratory response of the 3 subjects to whom barbiturates were administered contrasted sharply with that noted after the opiates. None showed a significant alteration in pCO_2, there was no definite pattern of respiratory depression as evidenced by respiratory rate, tidal or minute volume, nor was the response to carbon dioxide reduced after the barbiturate. The effectiveness of the drug as a sedative was unquestionable, since sleep was produced in all 3 subjects.

The sensitivity of the respiratory center to carbon dioxide is one of the protective mechanisms of man. Under the influence of sleep, narcosis, or coma it is one means for maintaining normal respiration. Normally, if the carbon dioxide is increased, respiratory effort likewise increases. It is this effect plus that of anoxia that enables a patient to "fight through" respiratory obstruction, overcome hypoventilation, or "break through" apnea. Depression of the respiratory center by opiates diminishes the ability of the patient to withstand or overcome these respiratory complications.

Fortunately, man has sufficient reserve to withstand considerable depression without harm. Under certain circumstances, however, his reserve may be diminished. For instance, the patient with pulmonary emphysema usually has an elevated pCO_2 and a diminished respiratory response to carbon dioxide. If opiates are administered to such patients, the pCO_2 is further increased, the respiratory response to carbon dioxide further diminished, respiratory acidosis enhanced, and a situation potentially hazardous to the patient is precipitated. Any

patient in whom the blood supply or function of the respiratory center is impaired (e.g., cerebral arteriosclerosis, cerebrovascular accident, senility, congestive heart failure) is a potential candidate for the same hazard.

Depression of the response of respiration to carbon dioxide is one of the more prolonged effects of opiates. Our data indicate that it persists after respiration appears to have returned to normal. For instance, subject M. S. (Table IV) demonstrated a 38 per cent reduction in response to carbon dioxide 5 hours after administration of meperidine, yet his control respiratory functions were interpreted as having returned to normal.

There are many data available to emphasize the protracted action of opiates. The prolonged duration of lethargy, vertigo, and nausea observed herein provide further support. The persistent elevation of pCO_2 after opiate administration is apparent among our data. The extended depression of respiratory response to accumulation of carbon dioxide fits into the general pattern.

Following the use of opiates, man can withstand other depressants less well. This is commonly observed in anesthetized individuals. Patients to whom opiates are administered preanesthetically often develop apnea following induction of anesthesia with cyclopropane, whereas apnea appears infrequently if opiates have been omitted from preanesthetic medication. The implication is that if a patient is under the influence of a depressant such as a general anesthetic, administration of an opiate may lead to an unexpectedly acute respiratory depression. This we have observed commonly in patients incompletely reacted from general anesthesia, yet complaining of pain.

Opiates are probably one of the most valuable group of drugs available to the physician. This report should not be construed as an attempt to belittle their importance. However, it should warn against their indiscriminate use, particularly in hospital practice. The ease with which opiates can be administered, their potency and their prolonged action comprise hazards to certain patients. The important action of opiates is analgesia; this should be the prime indication for their use. Barbiturates appear to be less hazardous and equally effective in producing sleep and relieving emotional stress. The routine use of opiates for preanesthetic medication is a questionable practice. We are at present engaged in investigating this problem. It appears that while deletion of opiates from preanesthetic medication is worth while, other difficulties may arise because of their omission. These observations require further assessment.

In clinical practice, a 4 hour period is often taken as the duration of action of opiates and is the basis for the "P.R.N" order. This is an unsafe and unwarranted assumption. Reduction in respiratory rate is likewise held to be a reliable indication of opiate effect. This also is not true except when large doses have been administered. Neither does the return of pain necessarily signify the end of all opiate effect. Significant respiratory depression can exist in spite of persistent or recurring pain.

Opiate administration requires individualized assessment of the patient. It should be with full cognizance of what the chosen narcotic may do to that particular patient. It requires reasonably constant surveillance. It should be for the relief of pain specifically. Only by the observance of these precautions can acute respiratory depression following injection of narcotics be prevented.

SUMMARY

Data obtained in man have been presented demonstrating the prolonged respiratory depressant effect and other side effects of morphine, meperidine, codeine, alphaprodine, dromoran, dihydromorphinone, and methadone. These data have been compared with similarly obtained observations with secobarbital.

Elevation in "alveolar" pCO_2, depression in respiratory minute volume, and reduced respiratory response to elevation in "alveolar" pCO_2 have been shown to be an invariable accompaniment of opiate administra-

tion. Respiratory rate was found to be an unreliable clinical index of respiratory depression by opiates.

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SURGERY IN THE PRESENCE OF THE THERAPEUTIC EFFECT OF DICUMAROL

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FOR MANY YEARS NOW the therapeutic usefulness of the anticoagulant drugs has been evident. In our experience in the past there were many occasions when the need for surgery arose either concomitantly with the desire to prescribe anticoagulant drugs, or in the course of having prescribed them. Because at that time, to the best of our knowledge, no precedent had been established for the practice of performing surgery safely during anticoagulant therapy, we realized the need and investigated the subject. It had long been our practice in thinking to consider coagulation and hemostasis synonymous. Because of this confusion and the threat of hemorrhage we had previously been afraid to operate upon patients with low prothrombin levels. However, in studying the subject we soon found good authority to allay some of our fears, incite our interest, and encourage us to venture some surgery in the presence of the therapeutic effect of an anticoagulant.

Coagulation of the blood is only one part of the hemostatic mechanism. The factors involved in hemostasis may be grouped under three classifications: extravascular, vascular, and intravascular factors. In a consideration of the intravascular factors three phases are involved: platelet massing, formation of a fibrin network, and contraction and hardening of the platelet and fibrin plug. Each of these intravascular phases may occur independent of the other or each fail to appear.

The sequence in achieving hemostasis is first the vascular response of the body which includes contraction of the injured vessel or its parent trunk vessel, a drop of pressure within the vessel, retraction of the vessel, and collapse and agglutination of the vessel walls. In smaller vessels clotting may not be necessary as the agglutination will maintain the occlusion of the vessel. If blood escapes into the surrounding tissue, there will be an increase in surrounding tissue tension with resultant compression of the injured vessel.

The second phase is the hematogenous phase. This is entirely dependent on the vascular response. Without slowing of the circulation, stasis, the blood would pass through the open vessel too rapidly either to build up a platelet plug or to allow time for accumulation and reaction of intravascular elements to form a clot. The coagulation time in vivo is normally between 30 and 90 seconds. Coagulation, therefore, could not of itself achieve hemostasis from the mouth of an open vessel because by the time 1 minute elapsed the flow of blood would have carried the initial efflux far from the mouth of the vessel making it ineffective in controlling hemorrhage.

MATERIALS AND METHODS

On the peripheral-vascular surgical service at The Bronx Hospital from January 1, 1949 to July 1, 1952, 60 patients had been subjected to surgery other than varicose vein ligation. Some of these patients had been treated preoperatively with anticoagulants, others received no anticoagulant, and some received an anticoagulant concomittantly with surgery. It is these 60 patients who have been selected for this study. Many controversial points may arise in a perusal of the tabulated case material but in this article no attempt will be made to discuss

TABLE I.—GROUP A, PATIENTS OPERATED ON WITH LOW PROTHROMBIN LEVELS

Patient	*Age Sex*	*Diagnosis*	*Operation*	*Duration of operation, Mins.*	*Time**	*Drugs used*	*Postoperative course*
1 M.R. 231236	70 M	Bilateral phlebothrombosis Three episodes of pulmonary infarct	Bilateral femoral vein ligation	105	35	Dicumarol	Uneventful
2 G.H. 232583	48 M	Thromboangitis obliterans Phlebothrombosis deep veins lf. leg Pulmonary infarcts	Inferior vena cava ligation	55	26	Dicumarol, depoheparin 200 mgms.	Uneventful
3 E.G. 240005	58 F	Dicumarol treated— Superficial thrombophlebitis Developed mesenteric thrombosis with gangrene transverse colon	Mikulicz resection transverse colon 1st stage followed by resection of exteriorized loop 2nd stage	50 30	30 30	Dicumarol Dicumarol	Uneventful Uneventful
4 F.T. 234581	66 F	Arteriosclerosis obliterans Status post midleg amputation, left Hypertensive cardiovascular disease	Right midthigh amputation (no tourniquet)	65	25	Dicumarol	P.O. gangrene both stumps, mottled cyanosis and coldness up to inguinal ligaments. Died 6th P.O. day. Imp.: thrombosis at bifurcation of aorta. No autopsy
5 A.G. 221928	65 F	Coronary thrombosis Pulmonary infarcts Bilateral femoral thrombophlebitis	Bilateral femoral vein ligation	75	29	Dicumarol	Uneventful
6 F.L. 234256	70 M	Arteriosclerotic heart disease Arteriosclerosis obliterans Gangrene left foot	1. Amputation left leg 2. Rt. lumbar sympathectomy	75 80	23 21	Dicumarol Dicumarol	Wound healed per primam Uneventful
7 A.S. 235216	75 F	Diabetes mellitis Arteriosclerosis obliterans Ulcer left heel	Midthigh amputation left leg	22	31	Dicumarol	Serosanguineous drainage from stump with gangrene of posterior flap. Revision of stump required
8 T.M. 235215	70 M	Benign prostatic hypertrophy Thrombosis left femoral artery	Left lumbar sympathectomy	60	37	Dicumarol	Uneventful. 18 days P.O. had cystostomy. 5 days P.O. had coronary occlusion and died
9 H.H. 244591	60 F	Rheumatic heart disease, auricular fibrillation Bilateral femoral emboli	Bilateral femoral embolectomy Left lumbar sympathectomy Rt. lumbar sympathectomy	90 55 70	Dicumarol and depoheparin given at time of operation 51 22	 Dicumarol Dicumarol	Uneventful Uneventful Uneventful
10 J.B. 245216	61 F	Diabetes mellitis Arteriosclerosis obliterans Cellulitis rt. foot Draining sinus head of middle metatarsal rt. foot Osteomyelitis	1. I & D and saucerization plantar surface, rt. foot, 1-11-52 2. Rt. lumbar sympathectomy, 1-14-52	25	32	Dicumarol	Slough of plantar wound separated leaving a clean granulating surface. Abdominal wound healed per primam
11 C.M. 249830	75 M	Benign prostatic hypertrophy Bilateral femoral phlebothrombosis	Bilateral common femoral vein ligation	80	35	Dicumarol	Hematoma left wound. Right wound healed per primam
12 S.R. 263473	68 M	Peripheral arteriosclerosis Five inch ulcer on dorsum rt. foot	Rt. lumbar sympathectomy Split thickness skin graft to ulcer	100	23 35	Dicumarol Dicumarol	Uneventful Uneventful
13 I.H. 266230	74 M	Myocardial infarct Auricular fibrillation Rt. popliteal embolus	Rt. lumbar sympathectomy	70	30	Dicumarol	Uneventful

*Prothrombin time in seconds at the time of operation.

Note: Cases 12 and 13 are included in this chart for the added weight of clinical experience they afford, although they were executed after July 1 1952.

these points, i.e., other than the point in question, our experience with some surgical procedures under the condition of controlled hypoprothrombinemia.

Of these 60 patients 11 or 18 per cent whom we shall refer to as group A, at the time of surgery had what is ordinarily considered a prothrombin level within therapeutic limits. Six or 10 per cent, group B, were treated with dicumarol simultaneously with the execution of surgery. It is primarily with these two groups of patients that our report is concerned, more particularly with the first group. The remaining 43 patients or 72 per cent, group C, have been utilized as a control series to compare complications and mortality as almost all of these patients were treated by the resident surgeons using similar techniques, under the direction of one man (J. K. L.).

CLINICAL RESULTS

In group A, Table I, are presented the patients subjected to surgery with low prothrombin levels. The youngest patient was 48 years of age and the oldest was 75. The average age of the group was 65 years. There were 5 men and 6 women. Fifteen operations were performed on these 11 patients while they were being treated with dicumarol; 4 patients had two separate operations during the period of anticoagulant therapy. Two patients of this latter group had an additional third operation one of which, a bilateral femoral embolectomy was performed simultaneously with the administration of depoheparin (Case 9) and the other after anticoagulant therapy had been discontinued. The following operations were performed: lumbar sympathectomy in 5 cases, major lower extremity amputation in 3, bilateral femoral vein ligations in 3, inferior vena cava ligation in 1, saucerization for osteomyelitis in 1, Mikulicz resection of transverse colon, first stage in 1, and Mikulicz resection of transverse colon, second stage in 1 case.

The prothrombin time varied in these 15 operations from a high of 51 seconds to a low of 21 seconds, the normal control being between 14.5 and 15 seconds. Although a few of the patients had a hypoprothrombinemia not ordinarily considered therapeutic with the administration of dicumarol, they are included in the group as they are still within the range that would ordinarily give the surgeon concern in terms of a contemplated surgical maneuver. It was with this concern in mind that we believed it important to report our results. These cases are included in Table I. In all of these cases dicumarol was used as the anticoagulant. Because of the concomitant urgency of the need for surgery and anticoagulation in some cases, depoheparin and dicumarol were initiated simultaneously, the former being discontinued when therapeutic levels of the latter were achieved. The operating times are listed in the table to indicate that they were not prolonged and that achievement of hemostasis at the time of surgery did not delay the procedures.

In the group of 11 patients there were 2 deaths neither of which could be ascribed to the use of the anticoagulant. Paradoxically in Case 4, although no autopsy was performed, the clinical picture in exodus was of a thrombosis at the bifurcation of the aorta, an eventuality which might not have occurred had more vigorous anticoagulant therapy been used. The other mortality, Case 8, occurred after complete recovery and per primam healing of the wound. Eighteen days after a lumbar sympathectomy this patient had a cystostomy. Five days later he developed a coronary occlusion and died. During this latter operation anticoagulant treatment had been discontinued. This operation is not considered in the tabulation of group A. In 2 of the patients in this group there was increased postoperative morbidity. One patient, Case 7, had a midthigh amputation and developed gangrene of the posterior amputation flap which required revision of the stump. Case 11 was interesting in that bilateral common femoral vein ligations were performed simultaneously by two teams. At

the time of surgery the prothrombin time was 35 seconds and on subsequent days 54, 54, 72, and 34 seconds, respectively. The normal coagulation time was 14.5 to 15 seconds. In this patient it must be assumed that the same coagulation and hemostatic mechanisms were operating on both sides, the only variable being the intervention of different surgical teams on each side. The right wound healed per primam and in the left wound a hematoma developed, the only complication in the group which was directly referable to the anticoagulant therapy. However, because of the nature of the control on the right side we believe that inadequate surgical hemostasis by the left team, not the hypoprothrombinemia, accounted for the hematoma.

In the present review of our results we are interested not in whether the surgery modified the course of the disease but only in ascertaining if, how, and to what extent anticoagulants modified certain operative procedures. Thus, in the 15 operations performed on the patients in group A, 12 wounds healed per primam, 1 patient died following the operation (a 9 per cent mortality), 1 amputation required revision, and a one-sided hematoma developed in a bilateral femoral vein ligation.

Group B includes the 6 cases treated by anticoagulant therapy and surgery simultaneously. They do not represent a new experience but are included for the sake of completeness in order to evaluate the clinical material from the peripheral vascular service from January 1, 1949 to July 1, 1952, from the point of view of anticoagulant therapy. The oldest patient in this group was 83 years old and the youngest was 22 years old. The average age was 57 years. There were 4 women and 2 men. Six operations were performed in this group as follows: bilateral femoral vein ligations in 2 cases, unilateral femoral vein ligations in 2, midleg amputation in 1, and internal fixation of intracapsular hip fracture in 1 case.

All of these patients were treated simultaneously by surgery and dicumarol. However, there was considerable variation in the sensitivity of these patients to the drug. The immediate postoperative prothrombin times were so variable and the group is so small that no conclusions can be drawn. However, isolated cases in which the levels rapidly dropped, as in 3 of this group, are of interest in that no hemorrhagic manifestations presented themselves. All of these patients had uneventful convalescences.

The cases in group C are presented as a control series. The group consists of the remaining patients operated upon by the peripheral vascular surgical service during the 3½ year period under study. None of these patients were treated with anticoagulants in relation to the surgery. The oldest patient in this group of 43 patients was 84 years old, the youngest 38. The average was 64.7 years. There were 25 men and 18 women. The operations performed in this group were as follows: unilateral lumbar sympathectomy in 28 cases, bilateral in 6; major amputations in 12; revision of amputation or reamputation in 4; amputation of a toe in 4; bilateral femoral vein ligation in 2; skin graft in 1; excision of aneurysm of ulna artery in 1; inferior vena cava ligation in 1; débridement and closure of ulcer in 1.

Sixty operations were performed on 43 patients in this group. Thirteen of these patients each had 2 operations, and 2 of the patients had 3 operations.

In group C there were 2 deaths, a mortality rate of 4.7 per cent. One of these patients died 9 days postoperatively after developing uremia during the postoperative period. The other died of a pulmonary embolus on the second postoperative day.

In this group of 60 operations 3 wound hematomas developed. One was in a lumbar sympathectomy wound; in a second patient a hematoma developed in a lumbar sympathectomy; later another hematoma occurred in an amputation stump. One patient developed a cerebral thrombosis on the fourth postoperative day from which she recovered. Of the 12 major amputations 4 required revision.

A comparison of the results obtained in group C and group A shows them to be parallel. In group A the mortality rate was 9 per cent, in group C, 4.7 per cent. In group A there was 1 wound hematoma in 15 operations; in group C, 3 hematomas in 60 operations. Of 3 major amputations in group A, 1 required revision; of 12 major amputations in group C, 4 required revision. Because of these results and our experience in handling the patients in group A, both on the operating table and in the postoperative period, we believe that there has been no added mortality or morbidity due to the concomitant use of controlled preoperative dicumarol therapy and surgery.

DISCUSSION

From a review of the clinical material and discussion of the mechanism of hemostasis, it can be seen that from both a practical and a theoretic point of view the concomitant execution of some surgical procedures while the patient is being treated in a controlled manner with dicumarol is feasible. The prothrombin time should not be prolonged for more than 70 seconds. In this situation coagulation does occur but is delayed. In those vessels, larger arteries and veins, in which coagulation is essential for the maintenance of hemostasis, the other hemostatic mechanisms are effective for a long enough period to contain the blood so that delayed coagulation occurs in time to prevent hemorrhage. It is not the coagulation time that is important in the maintenance of hemostasis but the formation of a tough, tenacious clot. In the smaller vessels, coagulation is not the important factor in achieving hemostasis.

We are not without precedent experience in studying hemostasis with dicumarol therapy. Zucker in 1947 studied rats in which the prothrombin time (Quick method) was increased from a normal value of 19 to 20 seconds to values ranging up to 34 seconds by the oral administration of dicumarol. Hemostasis was normal in these animals except for an increased incidence of delayed bleeding which was of no statistical significance. The lowest prothrombin level in her series of experiments was slightly over 20 per cent of normal. In 1948 Chen and Tsai showed that if blood was rendered incoagulable with dicumarol, constriction in arteries checked the immediate hemorrhage. However, when the arterial spasm relaxed, bleeding continued. Under their experimental conditions dicumarol was prescribed in excess of therapeutic levels delaying the coagulation time beyond the safe point. Tocantins states that there is normally a 5 to 10 fold excess of prothrombin over the amount required to bring about prompt coagulation of blood. Other factors being equal, a diminution of prothrombin level about 10 per cent of normal or below is necessary before a significant change is observed in the rate of clotting and quality of the clots formed. In our cases the level of prothrombin never descended to this low range. In 1951 in a discussion of the surgical treatment of carotid body tumors, Pemberton and Livermore reported the utilization of anticoagulants to prevent the late complications of ligation of the internal carotid artery. They first used this technique in January 1943. Up to the time of publishing their report they had used anticoagulants in 4 cases of carotid body tumors and in 1 case of aneurysm of the common carotid artery. In all 5 cases the common, internal, and external carotid arteries were permanently occluded. They prescribed 300 milligrams of dicumarol 12 to 15 hours before operation and heparin was started when the patient was on the operating table. They attempted to keep the coagulation time between 15 and 20 or 25 minutes. Dicumarol was continued orally to maintain prothrombin activity between 10 and 30 per cent of normal. They report no unusual difficulties because of the anticoagulant therapy. In Case 2 of their series in which dicumarol was used prophylactically a wound hematoma developed which subsided on conservative treatment. In 1952 Van der Veer, Parker, and Boyer reported an emergency appendectomy in a patient who had been receiving anticoagulants for a myocardial infarc-

tion. Because of fear of hemorrhage they prescribed large doses of vitamin K_1 oxide and citrated whole blood immediately preoperatively. However, 15 minutes prior to the execution of the surgery the prothrombin time was 24 per cent of normal. They reported no unusual bleeding and recovery from the operation was uneventful. Because of their therapy, however, the prothrombin time was 68 per cent of normal on the morning after surgery. McAllister, Leighninger, and Beck in their preliminary work on dogs in attempting to revascularize the heart by a vein graft from aorta to coronary sinus used dicumarol 2 to 5 days preoperatively. These dogs were maintained on the drug for 5 to 7 days postoperatively. They reported that oozing at operation was moderately severe but minute attention to ligation on opening and closing the chest permitted completion of the operation without undue blood loss. In some of their cases uncontrollable hemorrhage from the suture holes in the aorta during operation and in others postoperatively led to a fatal outcome. In all, they treated 28 dogs with dicumarol. The authors attributed 8 deaths to the anticoagulant therapy. However, they made no note of the prothrombin levels in any of these dogs except that an attempt was made to keep the levels below 20 per cent of normal. Could some of these dogs have been more sensitive to the drug in view of the fact that others tolerated the anticoagulant well?

SUMMARY AND CONCLUSIONS

That certain types of surgery can be performed with safety on patients who have prolonged prothrombin times has been demonstrated. In order to verify this theory, two avenues of approach have been taken. The mechanism of hemostasis has been reviewed with consideration given to factors other than coagulation responsible for retaining the blood. The role of delayed coagulation has been discussed.

A review of clinical material in which this thesis was tested is also presented. In all, in a 3½ year period, 15 operations were performed on patients who had prolonged prothrombin times. The results in terms of morbidity and mortality in this group are compared with those obtained in all other operations performed on the same surgical service in the same period of time. The results in the two groups are approximately the same. We have been able to execute some types of surgical procedures with therapeutically induced hypoprothrombinemia with safety. For the most part these procedures have been in relation to peripheral vascular disease. We do not draw the conclusion that all types of surgery can be safely performed under the condition of a therapeutically induced hypothrombinemia, as different hemostatic problems may arise in different surgical procedures. We can only report the experience that we have had.

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ADRENAL CORTICAL FUNCTION IN HYPOTHERMIA

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THE APPLICATION OF HYPOTHERMIA to the problems of surgery represents a real advance in technique. The advantage of hypothermic surgery arises from the decreased oxygen requirement of tissues at lower temperatures, permitting more prolonged periods of hypoxia in prolonged operations. Cooling results in a depression of metabolism in any organ or tissue, and a previous report from this laboratory has established that there is a depression in adrenal cortical function in general hypothermia (1). However, the unique role of the adrenal cortex in the body's response to injury in any form, as well as the fact that adrenal corticoid output is dependent on pituitary secretion of ACTH, makes necessary further exploration of the various factors involved. In order to accept cold per se as the basic mechanism of the adrenal cortical depression observed in this study, it must be shown that pituitary secretion of ACTH does not decline while the adrenal is still reactive. It must, furthermore, be demonstrated that the depression observed is not due to other general features of hypothermia, such as decreased blood flow to the adrenal gland, change in hydrogen ion concentration, or hemoconcentration.

The primary purpose of the present study is to characterize the adrenal cortical reaction pattern during the induction of hypothermia and rewarming. The rate of functional return upon rewarming has major clinical significance as does the magnitude of changes observed at various temperatures. The increasing use of generalized hypothermia makes it necessary that there be a thorough understanding of these mechanisms.

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MATERIALS AND METHODS

Adult, male, mongrel dogs ranging in weight from 10 to 20 kilograms were used in all experiments. Either intravenous sodium pentobarbital or pentothal-induced ether anesthesia was used.

The lumboadrenal vein was cannulated, as described by Hume and Nelson (3), by placing a polyethylene cannula in the lateral portion of the right lumboadrenal vein, and a "choker" around the connecting vein between the adrenal and the inferior vena cava. It is possible, by this means, to obtain intermittent samples of adrenal venous blood. When the choker is tightened, adrenal venous blood flows out of the cannula, but with the choker relaxed the blood takes its normal course into the inferior vena cava. The cannula is flushed and kept filled between samples with heparinized saline. Most of the experiments in this series were performed acutely. The adrenal venous blood samples were analyzed for 17-hydroxycorticosteroids, according to the method of Nelson and Samuels (6).

Three methods of producing hypothermia were used. In the first, an anesthetized, adrenal cannulated animal was placed in a cold room at −10 degrees C. In the second, an external arteriovenous shunt was cooled by ice water at a temperature of approximately 4 degrees C. Ten feet of polyethylene tubing were used to connect the femoral artery and vein. The animals were given heparin intravenously, 2 milligrams per kilogram, and the tubing was immersed in an ice water bath. In the experiments utilizing an arteriovenous shunt, mean blood pressures were obtained by means of a strain gauge and recording potentiometer connected to a cannula placed in a femoral artery. The third method of cooling con-

TABLE I.—HYPOTHERMIA EXPERIMENTS IN WHICH AFTER OPERATION THE ANESTHETIZED ANIMAL WAS COOLED AND REWARMED

Dog No.	*Normothermic minute corticoid output (average), micrograms*	*Hypothermic minute corticoid output (average), micrograms*	*Hypothermic / Normothermic Per cent ratio*	*Normothermic minute adrenal venous blood flow (average), ml.*	*Hypothermic minute adrenal venous blood flow (average), ml.*	*Lowest temperature to which cooled, °C.*	*No. of corticoid determinations*	*Anesthesia*
1*	7.6	0.8	10.5	6.0	0.6	25.5	43	Pentothal-ether
2+	5.4	0.6	11.1	3.3	1.2	23.0	38	Pentothal-ether
3+	8.6	0.8	9.4	5.6	0.9	24.0	27	Pentothal-ether
4+	15.5	3.9	25.1	6.0	1.4	28.0	16	Pentothal-ether
5+	17.5	1.9	10.8	3.5	0.6	24.0	35	Pentothal-ether
6+	6.9	0.9	13.0	2.5	0.6	25.0	30	Pentothal-ether
7°	12.2	2.4	19.6	3.7	0.5	21.0	16	Pentothal-ether
8°	9.6	1.8	18.8	5.2	1.4	23.0	7	Pentothal-ether
9°	16.6	3.5	21.1	8.1	2.6	25.3	8	Pentothal-ether
10°	8.8	2.2	25.0	4.5	0.9	25.5	2	Pentothal-ether
11°	7.3	0.2	2.8	4.0	0.6	23.0	20	Nembutal

* - Air cooled.
\+ - External shunt cooled.
° - Ice water immersion cooled.

sisted of total body immersion in ice water at a temperature of approximately 4 degrees C.

In all experiments rewarming was accomplished by total body immersion in warm water at 45 degrees C. The animals were given positive pressure respiration at body temperatures below 30 degrees C. With all three methods of cooling, intermittent samples of adrenal venous blood were obtained at each degree centigrade drop in body temperature, measured by thermometers inserted at least 4 inches into the rectum. When adrenal venous blood flow reached a level of approximately 0.5 cubic centimeter per minute, the animal was rewarmed. In a few experiments, hypothermia was carried to a point at which adrenal blood flow ceased.

In several experiments the animals were given a continuous infusion of ACTH, 40 units per 1,000 cubic centimeters of normal saline, before and during induction of hypothermia and rewarming. In 1 instance, a single injection of 40 units of ACTH was given when the animal was hypothermic. In 1 experiment, 200 cubic centimeters of blood were withdrawn from a hypothermic animal, adrenal venous blood samples were taken, and the blood was then replaced. In 3 experiments the mean blood pressure was maintained at normothermic levels during the production of hypothermia by the infusion of a solution of norepinephrine, 8 milligrams per 1,000 cubic centimeters of normal saline. In another group of experiments, systemic normothermia was maintained by warming an arteriovenous external shunt while local cold was applied to the adrenal gland. Local cold was applied by infusing ice water into a condom placed on the gland.

In 2 experiments peripheral samples of blood were drawn in the normothermic and hypothermic states for ACTH assay according to the method of Nelson and Hume (5). In 1 animal the adrenal vein cannulation was performed under sterile conditions, and on the day following surgery, anesthesia was again induced and the animal was cooled. Intermittent samples of adrenal venous blood were obtained during induction of and rewarming from hypothermia.

RESULTS

The results of these experiments may be divided into six categories:

1. *Different methods of producing hypothermia and standard pattern of adrenal cortical response—11 dogs.* Table I summarizes the findings in this group of animals. Neither the type of anesthesia used, nor the rate of cooling or rewarming had any apparent influence upon the pattern of adrenal cortical depression in hypothermia. There is a progressive

and profound suppression of 17-hydroxycorticosteroid secretion in the adrenal venous blood of dogs cooled by any of the 3 different methods used. The decline in corticoid output usually begins at a rectal temperature between 34 and 35 degrees C., and the output continues to fall as the body temperature falls. Rewarming to normal body temperature results in complete return of corticoid secretion to normal or above normal levels. In about half the dogs a posthypothermic increase in corticoid output was seen compared to the prehypothermic levels. Although there was always a decrease in adrenal venous flow with hypothermia, a relatively greater reduction in corticoid output usually occurred.

A typical experiment is shown in Figure 1. The animal was cooled until the minute adrenal venous flow was approximately 0.5 cubic centimeter, and then rewarmed to body temperature. It can be seen that there was a considerably greater corticoid output after rewarming than in the control period. Furthermore, it is seen that the corticoid depression of hypothermia is not monotonic, but exhibits fluctuations superimposed on a general downward trend.

2. *Constant infusion of ACTH during hypothermia—10 dogs.* In Table II are shown the results obtained by cooling animals receiving constant infusions of ACTH during the induction of hypothermia and rewarming. These results differ in no significant way from those shown in Table I and demonstrate that there is a progressive and marked depression of adrenal cortical function in hypothermia despite the exogenous administration of ACTH. In most instances the start of the ACTH infusion resulted in an increase in minute corticoid output in excess of that obtained immediately after completion of the adrenal vein cannulation, particularly when nembutal anesthesia had been used.

Figure 2 illustrates the progressive fall in minute corticoid output during hypothermia, in spite of the constant infusion of ACTH. The corticoid output returned to normal values after rewarming.

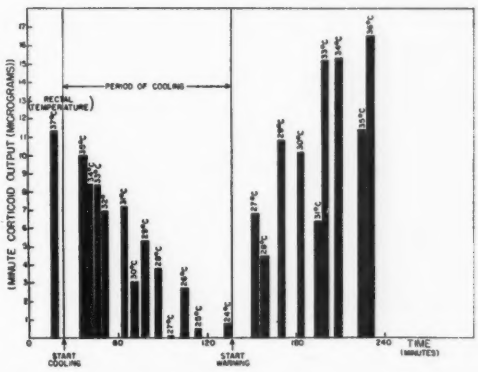

FIG. 1. Hypothermia experiment with external shunt cooling and rewarming.

In another experiment an animal was given an injection of 40 units of ACTH after cooling to 23 degrees C., and no significant increase in corticoid output resulted. In an effort to ascertain whether the adrenal cortex will respond to other stimuli, 200 cubic centimeters of blood were removed from 1 animal when the body temperature was 29.0 degrees C., and the minute corticoid output was 4.6 micrograms. Although the blood pressure fell from 75 to 45 millimeters of mercury as a result of the hemorrhage, the minute corticoid output also fell to a value of 3.7 micrograms.

3. *Blood ACTH assay during hypothermia.* Results of ACTH assay in 2 experiments revealed that there was a significantly decreased level of circulating ACTH in the hypothermic as compared to the normothermic animal. In 1 experiment blood was drawn for assay at 25 degrees C. body temperature and in the other at 23 degrees C.

4. *The maintenance of normal blood pressure during hypothermia.* In 2 animals, infusions of l-norepinephrine were given during the induction of hypothermia. Although mean blood pressures were maintained at or near the normothermic levels during the entire cooling procedure, typical depressions of corticoid output were obtained during hypothermia. It was observed that as body temperature fell to about 24 degrees C. there

TABLE II.—EXPERIMENTS IN WHICH AFTER OPERATION THE ANESTHETIZED ANIMAL RECEIVED ACTH INFUSION, DURING INDUCTION OF HYPOTHERMIA AND REWARMING

Dog No.	Normothermic minute++ corticoid output (average), micrograms	Hypothermic minute corticoid output (average), micrograms	Hypothermic / Normothermic Per cent ratio	Normothermic minute adrenal venous blood flow (average), ml.	Hypothermic minute adrenal venous blood flow (average), ml.	Lowest temperature to which cooled, °C.	No. of corticoid determinations	Anesthesia
12*	14.9	1.1	7.4	5.3	0.7	21.0	34	Pentothal-ether
13+	13.8	3.6	26.1	3.9	2.0	25.0	31	Nembutal
14+	13.9	0.7	5.0	3.4	1.2	25.0	27	Nembutal
15+	11.3	4.8	42.5	4.2	4.0	26.0	17	Nembutal
16+	19.9	0.9	4.0	4.5	1.1	21.5	31	Nembutal

* - External shunt cooled.
\+ - Ice water cooled.
++ - Receiving ACTH infusion during the sampling period.

was marked cardiac irritability and in 1 case ventricular fibrillation. Cardiac irritability was not observed in animals not receiving the norepinephrine infusion at body temperatures above 23 degrees C.

5. *The effect of cold applied locally to the adrenal.* In 3 experiments local cold was applied to the adrenal gland while systemic temperature was maintained at normothermic levels. In 1 of these experiments there was a marked fall in corticoid output but difficulty was encountered in maintaining normothermia so that it was impossible to determine whether the fall in corticoid production was due to systemic or local hypothermia. In 2 other experiments, the application of a condom with ice water irrigation to the adrenal gland resulted in a significant fall of minute corticoid output, despite the maintenance of body normothermia. One of these experiments is illustrated in Figure 3. It can be seen that local warmth results in very rapid return to normal minute corticoid values. In the 2 cases in which cold applied locally to the adrenal resulted in minute corticoid fall, mean blood pressure remained almost constant during the procedure.

6. *Is hypothermia a stress?* In 3 experiments, adrenal vein cannulation had been performed the previous day. After induction of anesthesia with nembutal, minute corticoid outputs were very low, ranging from 1.2 to 0.5 microgram. Usually minute corticoid outputs are very low the day after surgery in these basal, unstressed "chronic" cannula animals. Hypothermia was induced by ice water immersion. Minute corticoid outputs, during production of hypothermia down to body temperatures of 26 degrees C., were not above the control levels in both animals. In 1 animal there was some corticoid response upon rewarming, with a level of 4.5 micrograms at a body temperature of 35 degrees C. and 8.7 micrograms at 37.0 degrees C. Lowering the body temperature under nembutal anesthesia, therefore, did not appear to activate the adrenal cortex.

DISCUSSION

Since 17-hydroxycorticosterone is the principal adrenal cortical hormone secreted in the dog and man, the amount of this substance in adrenal venous blood was used as a measure of adrenal cortical activity. Our data indicate that there is a consistent and progressive decline in the amount of 17-hydroxycorticosteroids secreted from the adrenal gland as the body temperature is lowered. At body temperatures between 22 and 28 degrees C. corticoid outputs were reduced to 25 per cent or less of the normothermic levels. There is considerable variation in animals and it is difficult to generalize about the temperature at which adrenal cortical function ceases (1). Adrenal venous flows become greatly reduced at the lower temperatures, and often cease when the minute corticoid outputs are 5 to 10 per cent of normothermic levels. Neither the rate nor method of cooling appeared to influence this adrenal cortical depression. It occurs

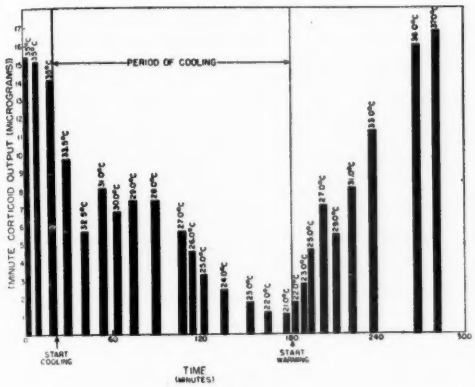

FIG. 2.

FIG. 2. Hypothermia experiment during which animal received constant ACTH infusion (external shunt cooling).

FIG. 3. Local cold on adrenal gland with systemic normothermia.

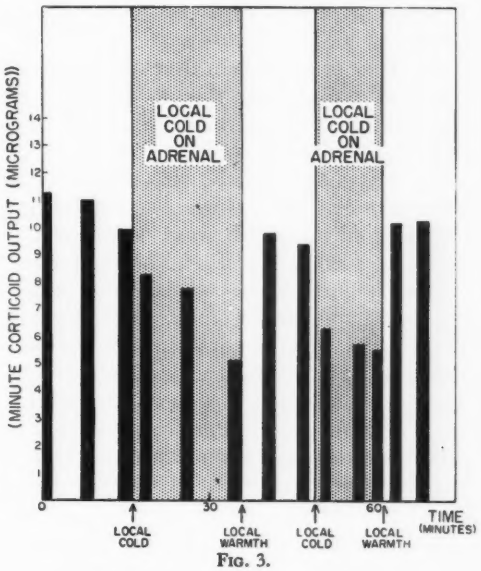

FIG. 3.

when the animal is anesthetized either with sodium pentobarbital or pentothal-induced ether anesthesia.

Georges and Cahn state that the pituitary fails to release ACTH in hypothermic states below 27 degrees C. and that exogenous ACTH must be administered to achieve an adrenal cortical response. They found adrenal ascorbic acid depletion in rats cooled as low as 22.5 degrees C. and given exogenous ACTH. Khalil also discovered no adrenal ascorbic acid depletion in rats cooled to 20 degrees C. without exogenous ACTH, and he concluded that the adenohypophysis does not release ACTH in hypothermia. In his study, administration of ACTH to rats hypothermic at 20 degrees C. resulted in adrenal ascorbic acid depletion to 25 per cent of normal. However, these results are based on indirect methods of assessing adrenal cortical function. With the direct methods of this study, we have found no change in the typical hypothermic pattern of adrenal cortical depression when the animals are given ACTH infusions during the hypothermic procedure. It has been shown that a prolonged maximal adrenal cortical stimulation is produced by a continuous ACTH infusion, surpassing the effect of either a single intravenous or intramuscular injection. This indicates that decreased pituitary secretion of ACTH, while perhaps present in hypothermia, is not the basic reason for the adrenal cortical depression here observed. Bioassays indicate that there is a marked decline in circulating ACTH during hypothermia, as compared to the normothermic levels.

It has been shown by Hume and Nelson (3) that adding the effects of hemorrhage to an animal already in a state of surgical stress results in an increased adrenal corticoid secretion. This increased corticoid secretion was shown not to be due to increased ACTH release by using hypophysectomized animals receiving constant infusions of ACTH, hence a potentiating effect on the adrenal was postulated as a mechanism of action. We produced a marked fall in blood pressure by the removal of 200 cubic centimeters of blood from a hypothermic animal with no resultant increase in corticoid secretion from the adrenal. So, not only is the cooled adrenal unresponsive to ACTH, but a known

potentiator of the ACTH present is without effect.

In order to be certain that the decreased corticoid output was due to the reduced temperature of the adrenal gland itself, and not to some other factor in hypothermia, the gland was cooled locally while maintaining normal body temperature. The marked fall in corticoid secretion from local cold is further evidence that a cold adrenal is unable to respond to the usual stimuli. Maintaining normothermic blood pressure during hypothermia by the administration of norepinephrine failed to alter the fall in corticoid output, which suggests that hypotension is not the factor responsible for adrenal suppression under these circumstances. Changes in blood hydrogen ion concentration were avoided by using positive pressure respiration during the hypothermic experiments.

It is significant that a complete return to normal corticoid output was observed immediately after the animal had been rewarmed. This fact indicates that the adrenal gland is not damaged by general hypothermia and that there is no lag in complete recovery of normal function. Furthermore, cooling of the unstressed, anesthetized animal demonstrated that hypothermia itself did not lead to adrenal stimulation, and therefore could not be included in the long list of "stresses" which are accompanied by increased adrenal cortical activity.

In a few preliminary experiments, adrenalectomized dogs were given injections of 17-hydroxycorticosterone at normal and hypothermic temperatures, and determinations of the rate of disappearance of the exogenous corticoid were made. Tentatively, we can say that utilization of corticoids appears to be decreased in the hypothermic adrenalectomized animal. Nothing is known, however, about the needs for corticoids when severe surgical trauma with blood loss is superimposed on the hypothermic state. This phase of the problem must be investigated before we can categorically say that the decreased adrenal cortical secretion seen in hypothermia does not result in a relative deficiency of these hormones in the tissues. However, it appears likely that there is not a deficiency in hypothermia, but rather a depression of ACTH secretion, adrenal corticoid output, and tissue uptake alike, with immediate return to normal values upon rewarming.

CONCLUSIONS

1. Hypothermia is accompanied by a marked depression of adrenal cortical secretion in the dog, as measured by adrenal venous blood minute output of 17-hydroxycorticosteroids.

2. The secretion of ACTH is also markedly depressed in hypothermia.

3. Adrenal cortical responsiveness to exogenous ACTH is sharply reduced in hypothermia, apparently as a consequence of the direct effect of cold on the adrenal and not as a result of hypotension or other known effects of general hypothermia.

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CHRONIC ULCER OF THE BLADDER ASSOCIATED WITH SCHISTOSOMIASIS

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THE PATHOLOGIC PROCESSES initiated by the schistosomal lesion continue many years after the disease has been clinically cured by repeated courses of antimony compounds and after viable ova are no longer being excreted in the urine. The aftermath of supposedly cured vesical schistosomiasis leaves a number of incapacities with a confusion of clinical signs and symptoms that are hard both to diagnose and to classify.

We, however, have been impressed by the constancy of the clinical and pathologic picture of ulceration of the bladder occurring in vesical schistosomiasis. In its course, remission, clinical signs, and pathology, the cases are similar and a definite clinical entity for this condition should be established.

MATERIAL AND METHODS

For this study, 33 cases are reviewed of patients who were hospitalized at the American Mission Hospital, Tanta, Egypt. The cases reported were of consecutive patients who submitted to subtotal or partial cystectomy. No criteria were established other than the positive identification of an ulceration of the bladder by cystoscopy and a history of treated schistosomal infection. The excised tissues from the bladder were examined grossly and placed immediately in 10 per cent neutral formalin solution and allowed to fix completely. Routine multiple sections were taken from the ulcer and surrounding tissues and processed for microscopic sections. Staining of the sections was accomplished by alcoholic eosin and hematoxylin, and Masson's trichrome method.

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The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

CLINICAL FEATURES

Distribution. The disease appeared more common in males; of 33 patients there were 26 males and 7 females. The average age was 29½ years; the youngest was 16 and the oldest 42 years old. Intensity of the original infestation did not seem to be a factor in the etiology, and the geographic distribution was not limited to the intensely infected schistosomal districts. Some of the patients had been infected in childhood and had since been living for many years in the larger cities where probably reinfestation would not occur. Religious customs also did not appear to have any effect on the occurrence of this ulcer. Patient occupation was predominantly agricultural.

Duration of symptoms. The average time that symptoms were present was 3 years, the shortest 8 months and the longest 10 years.

The sudden onset of gross hematuria was the most frequent symptom. The usual history was that the patient, having been previously asymptomatic suddenly began to urinate large quantities of "pure blood." In almost every case this was related to heavy physical effort or a long ride with a full bladder on a camel, horse, or donkey. A long ride in a motor car on a bumpy road has produced the same result. Microscopic hematuria was consistently present in all cases.

By history, the gross hematuria reportedly improved spontaneously on rest, dwindling

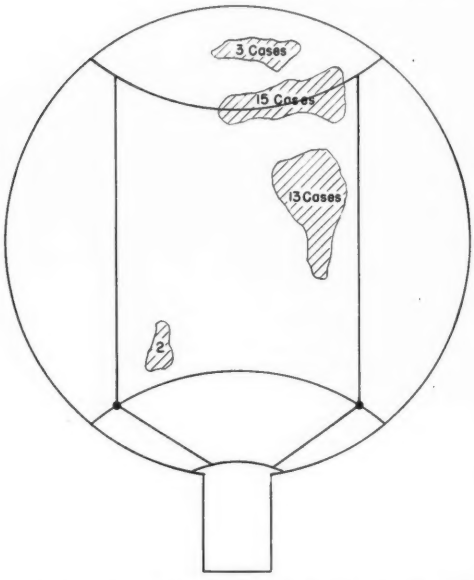

FIG. 1. Schematic drawing of the bladder showing the location of ulcers seen at time of operation.

in a few days to terminal hematuria, but it occurred again when the bladder became overdistended and heavy physical effort was undertaken. The recurrence of hematuria was unaffected by further antimony treatment.

Pain. There was a very definite relationship between the duration of the symptoms and the onset of pain. Thus it was almost nonexistent in patients who had a bladder ulcer for less than a year. Pain was reported by the patients to have increased with time. In those with ulcers of more than 4 years' duration, pain appeared to dominate the clinical picture. In its mildest forms the patient complained of dull pain with a varying degree of warmth in the suprapubic region. Progressively this dull pain occurred whenever the bladder was even partially filled and with defecation. As the disease progressed it radiated to the perineum as sharp stabbing pain with intense urethral itching reaching its maximum at the end of urination. Characteristically it increased on effort and became almost intolerable when riding horses or donkeys. It was reported rarely present at night and appeared usually during the day. In its severest forms, when the disease had a clinical course of several years, pain was only partially relieved by resection of the bladder ulcer.

Frequency was characteristically absent at night unless the disease was found in combination with a small capacity bladder with considerable pericystitis. In cases in which secondary infection was present, frequency was also present with dysuria. In a bladder with sterile urine, frequency was diurnal and dysuria was absent unless the patient was passing blood clots.

Spontaneous periods of remission were characteristically present in every early case. In the past this circumstance has lent encouragement to the use of cautery, bladder lavages, and antibiotics. Eleven of our patients were followed from 1 to 3 years and cystoscoped at 6 month intervals. Apparent healing of the ulcer occurred; but much to our surprise, at cystoscopy after a recurrence of symptoms, the ulcer was again seen bleeding and active.

Cystoscopic appearance. Distention of the bladder produced bleeding from the ulcer, more often than not, so severe as to obstruct accurate vision. Visualization was most satisfactory with no more than 2 to 3 ounces of water in the bladder. Most of the ulcers were present in the posterior wall above the left ureter and in the dome, or the expansile portion of the bladder where visualization was difficult (Fig. 1). Dilatation of the bladder to compensate for the decreasing capacity occurred in the trigone and the areas between the external and internal sphincters. As a rule the ulcer was linear, 1 to 2 centimeters in length with irregular but flattened margins, oozing blood, its base covered with a grayish membrane if infected, red, raw, and beefy if not. In the partially empty state of the bladder the ulcer margins may be irregular, elevated to fulfill the criteria of malignant change. When the bladders were distended to full capacities at the end of the examinations, the edges were ob-

FIG. 2. Roentgenogram of urinary bladder showing cal calcification of the wall beneath site of ulceration. ote asymmetry of bladder due to limitation of distention.

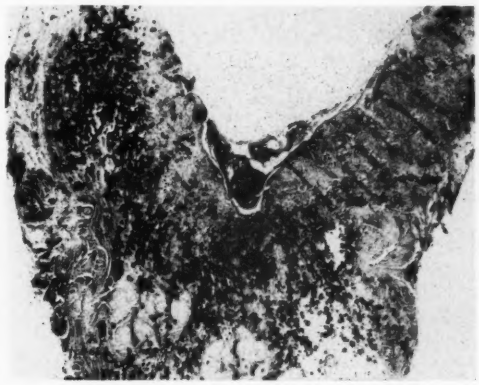

FIG. 3. Low power appearance of ulceration of posterior wall of the bladder associated with long standing schistosomiasis.

rved to flatten out. In our experience this a very important maneuver since if "its lges remain fixed and retain their irregular hape seen when the bladder is partially npty, it is a very strong argument that the lcer is a malignant one." Nevertheless, in ystoscopy of old cases, this maneuver may ot satisfy the differentiation between beignity and malignancy.

Treatment. Surgical excision is considered the treatment of choice after long and careful study of other methods of treatment currently in use in this geographical area. Eleven cases were followed for many months and in no instance could one say that a complete cure had ever been achieved without surgical excision. Furthermore, 2 cases under observation in this period of nonsurgical treatment showed definite malignant changes and 3 additional cases demonstrated repeated severe hemorrhage. Since then we have undertaken excision of the ulcer through a suprapubic cystostomy as the preferred treatment. This is in contradiction to a statement in a paper published by one of us in 1948(11).

In 33 patients treated by excision we have noted in the period of follow-up complete relief of gross hematuria, frequency, and dysuria in all cases. Pain radiation to the perineum, if present more than 4 years, has tended to persist after operation. Further treatment in these cases of persistent pain is beyond the scope of this article, but some gratifying results have been achieved by intrapelvic section of the nervi erigentes.

PATHOLOGY

Gross. The ulcers after surgical removal showed little change from the cystoscopic appearance. The ulcers were oval to elongated in shape. The margins varied from an irregular or serrated pattern to smooth soft lips. Overhanging margins were not present and a saucer-like configuration was the most common form. The bladder wall in the contracted state was thickened rather than thinned beneath the ulcerated site. The thickening usually extended for less than 5 to 10 millimeters from the ulcer proper. The ulcer base was hard. Edema was occasionally seen in the mucosa surrounding the crater. More often roughened mucosa was seen so commonly associated with vesical schistosomiasis. When grossly sectioned, a calcified plaque could usually be detected in the ulcer base. The gritty character appeared limited to the pale white thickened fibrotic mass that replaced the submucosa and internal half of the muscle. Changes were seldom found in the serosal portion of the resected specimens. The exact site of bleeding could

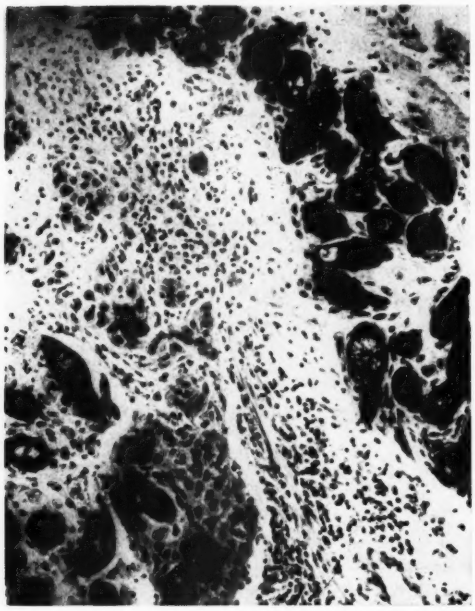

FIG. 4. Squamous metaplasia of bladder epithelium is diffuse, associated with ulceration of epithelium at upper left and extends about ova. Patient was treated for years with tartar emetic for schistosomiasis. ×405.

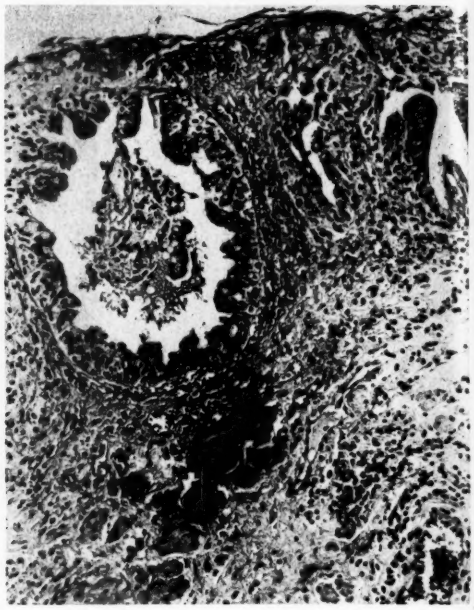

FIG. 5. The condition termed as cystitis cystica is present in the bladder in this case. The change is associated with long standing treated vesical schistosomiasis and ulceration. ×405.

not be detected in the gross specimen so that multiple sections for microscopic study were required. The ulcer base was gray in color if granulation tissue and hemorrhage were not pronounced. The early ulcers showed usually scarlet red bases covered by tenacious material.

Histologic examination. Thirty-one of the 33 cases were available for histologic review and classification. Four types of lesions were present that somewhat depended upon the density of ova in the bladder wall, the duration of complaint or known disease, the inflammatory reaction to the schistosomal ova, and reaction of the transitional cell epithelium to the ulcerative process. For histologic description of the disease, the four types present in this current series were as follow:

Type I. Early lesion—bilharzioma with active scarring.

Type II. Established lesion of short duration—granulomatosis with calcific plaque formation.

Type III. Late lesion of long duration—calcified plaque with deep scarring and attempted healing.

Type IV. Late lesion with neoplasm—calcified plaque with primary carcinoma.

Of the 31 cases in this series, 5 were type I; 13 were type II; 11, type III; and 2, type IV.

Type I. Bilharzioma with active scarring.—The size of the ulcers was usually small and the ulceration somewhat spotty or focal. The term "bilharzioma" was applied to the striking foreign body reaction to the trapped schistosomal ovum. The tissue reaction to form the bilharzioma was immediately about the ovum or ova cluster. The foreign body giant cells partly engulfed the ovum and contained high nuclear counts. The ovum usually showed some intermediate stage of degeneration or, in an occasional site, only the chitinous shell remained. The cells supporting the foreign body giant cells were

monocytic types with lymphocytes, plasma cells, and eosinophils. Epithelioid cells may be the most prominent component of the bilharzioma but frequently the chronic inflammatory cell reaction overshadowed the former cells type. Collagen tissue or organizing fibrous tissue was usually the outermost component of the focal process. This component varied markedly in degree and usually blended into that of an adjacent bilharzioma. In this component was usually a dense eosinophilic cell infiltration. Numerous bilharziomas composed this type lesion with a tendency to cluster in the center of the ulcer. The bilharziomas composed the ulcer base and only an occasional group of mucosal cells remained. When seen, the mucosal cells appeared within normal limits. The bulk of the process occupied the supporting or submucosal zone but rarely extended for any great depth into the muscular layer. Chronic inflammatory cells were occasionally seen in the fibrous tissue between the muscle bundle and periarterial or perivenous sites. Panarteritis was usually not present to any marked degree. The bleeding site could be detected by multiple sections and consisted of a diffuse hemorrhage rather than the rupture of large vessels. Little vascular hypertrophy was seen in this type. Nonviable ova of the Schistosoma haematobium were observed in all cases of this type as well as in 2 cases which showed viable ova.

Type II. Granulomatosis with calcific plaque formation.—This type of ulcer was usually observed in the well established lesions or lesions older than type I. The schistosomal foreign body process was replaced entirely by a granulating base. Foreign body reaction was absent and hypervascularization, scarring, and calcification were the important processes that replaced it. In general the ulcers had broader bases and penetrated deeper. The granulomatous bases did not always contain viable or degenerating schistosomal ova. The granulation tissue was rich in newly formed blood vessels and the site of hemorrhage could

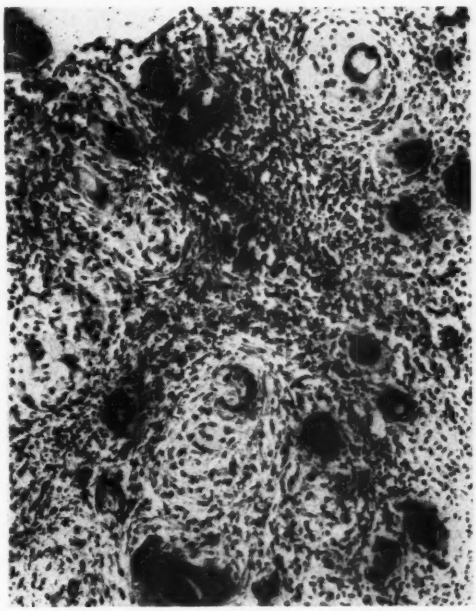

FIG. 6. Ulceration of the bladder type I showing numerous bilharziomas. Note the trapped ova of Schistosoma haematobium. ×405.

usually be detected in the microscopic serial examinations. Again the hemorrhage from this type of ulcer was in the form of diffuse bleeding from the capillary bed. Inflammation was a prominent feature, usually a mononuclear type with plasma cells predominating. The deeper portions of the ulcers showed active scarring with an abundance of fibrous connective tissue separating the muscle bundles. The calcific plaque was in the stage of organization and in most cases existed through the submucosal layer in the ulcer zone. The calcification was focal and ova density was not advanced as type III. The ova showed various stages of degeneration to the degree of mass calcification. Frequently only a portion of the ova was calcified and the remaining ova showed late degenerative or amorphous changes. Frequently cystitis cystica was present and early stages of metaplasia were observed both in these glands and in the topical epithelium. Only 5 of the 13 cases of this type

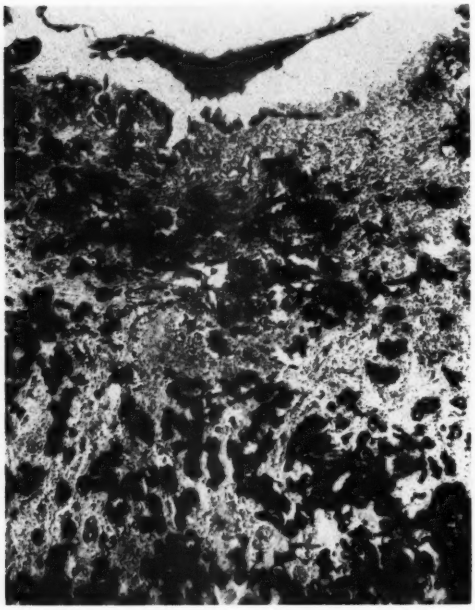

FIG. 7. Ulceration of the bladder type II showing granulation tissue base. Note the fibrous tissue and forming calcific plaque beneath the base. Ghost outlines of ova resemble Schistosoma haematobium. ×70.

ulcer showed metaplasia and 5 showed extensive cystitis cystica formation in the presence of chronic inflammation. In 3 cases there was a well defined adenoid pattern.

Type III. Calcified plaque with deep scarring and attempted healing.—This type of ulcer showed an old process or at least one of long duration. In the ulcer proper, the base consisted of a rather superficial dense calcific plaque that was composed of innumerable oval forms that represent the once viable ova of the schistosome. In most cases observed, this plaque was gritty and hard to section but decalcification by acids or electrolytic means was not required. The individual ova were replaced by calcium salts but rarely showed coalescence. This plaque was relatively avascular as was the voluminous dense fibrous tissue beneath it. The plaque often was the ulcer base proper but frequently a thin layer of fibrous tissue enveloped it. Since this fibrous tissue was practically avascular, attempts of repair of the rent in the mucosa were not successful. The mucosa was hypertrophied about the margins of the ulcer and frequently showed small polypoid projections that were squamous or adenoid if metaplasia had occurred. Metaplasia of the transitional type epithelium was frequent. The fibrous tissue present beneath the calcified ova mass extended to, and often into, the muscle layer. The muscle bundles showed atrophy and encasement by the dense fibrous tissue. Ova of the schistosomes were frequently seen in these deep projections of fibrous tissue. If viable or degenerating ova were present, they were usually observed in the epithelium and submucosa surrounding the ulcer. In these sites, granulomatous foci and even bilharzioma were observed providing a wide excision had been made. Inflammation in the ulcer and fibrous tissue was not usually marked and occasionally was entirely absent. Vessel dilatation was occasionally seen but in some cases was attributed to muscle atrophy and relative prominence of the vascular structures.

Type IV. Calcified plaque with primary carcinoma.—This type ulcer usually followed that of types II and III. The distinguishing feature was the presence of carcinoma. The carcinomas of this current series were transitional and adenoid cell types and contained many degenerated and calcified ova of Schistosoma haematobium. The finding of ova in the carcinomatous growths was not unusual. Other studies in progress at this research facility in regard to carcinoma of the bladder in schistosomiasis show that the majority are associated with ulceration and contain schistosomal ova in varying degrees. The site of infiltration follows immediately beneath the site of the ulcer into the bladder wall and along the submucosal zones beneath the intact epithelium. The calcific plaque remains intact and serves as an indication and extent of primary ulceration. This type of lesion constitutes the most serious complication of schistosomiasis of the bladder. Hematuria was of

he same type clinically as seen in the type II ulcer.

ATHOGENESIS OF CHRONIC ULCER OF THE LADDER IN SCHISTOSOMIASIS

The onset of the infestation of schistosoiasis is the beginning of the process which eads to ulceration of the bladder. Since chistosoma haematobium infestations are sually the type that inhabit the veins in nd about the bladder, this type of infesation is thought to be essential. In the curent series all bladders showed Schistosoma aematobium type ova only. The occasional chistosoma mansoni that has been found n the bladder wall has not been observed t this laboratory in association with ulcers urgically removed. After the infestation by he schistosomes has been established the ormal course of ovum production begins. The eggs are deposited in the terminal enules and start their migratory course toward the lumen of the bladder. Tissue rection in the form of a mild inflammatory ell reaction occurs as soon as the ovum nters the extravascular spaces. Focal hemorrhage occurs at the site of migration and usually can be followed to the exit site in he transitional cell epithelium. Minute scarring occurs along the ovum's path. Small clusters of ova usually follow along the same or an immediately adjacent path. As succeeding ova migrate from the site of deposition, increased tissue resistance is present because of the multiple small foci of scar tissue. Many of the ova find it too difficult to withstand successfully the migration to the lumen and, along with the nonvital ovum deposited, became lodged in the bladder wall. These forms degenerate in the bladder wall and are usually located in the submucosa and epithelium. Foreign body reaction and marked eosinophilic cell infiltration occur and may proceed to form the well defined tubercle previously referred to as bilharzioma. As more ova degenerate in the bladder wall, the tissue reaction becomes more acute and widespread. The end product of the foreign body reaction is that of calcification of the ovum or absorption. Although numerous chitinous fragments of the schistosomal ova are observed in the colon and the liver, few are seen in the bladder wall. In the bladder the usual final state is calcification to such an extent that the outline of the entire ovum is preserved. The accumulations of scar tissue or calcified ova diminish the vascular bed and in turn devitalizes the transitional epithelium.

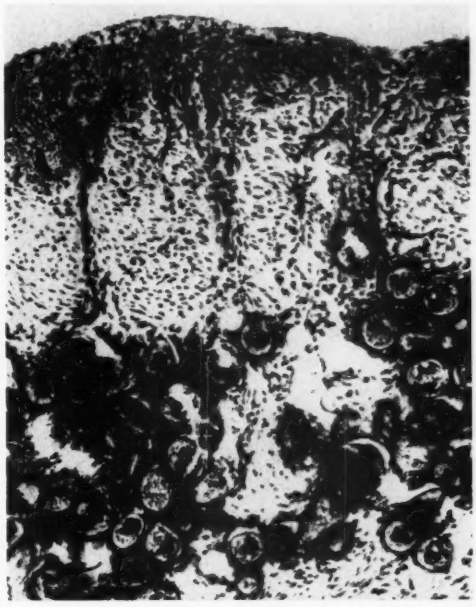

FIG. 8. Ulceration of the bladder type III showing the relatively avascular fibrotic base and established calcific plaque of Schistosoma haematobium ova. ×202.

Ulceration begins with the normal migration of the ovum but this type ulcer is minute and accompanied by little gross hemorrhage. However, if many such minute ulcers occur gross hematuria as well as constant microscopic hematuria will be present. Further, if the ova are concentrated in a small area of the bladder wall and the number is large, minute ulcers may fuse and form a large ulcer that results in gross hematuria. This type of ulcer when accompanied by the foreign body reaction to the degenerating ova is classified as type I. The

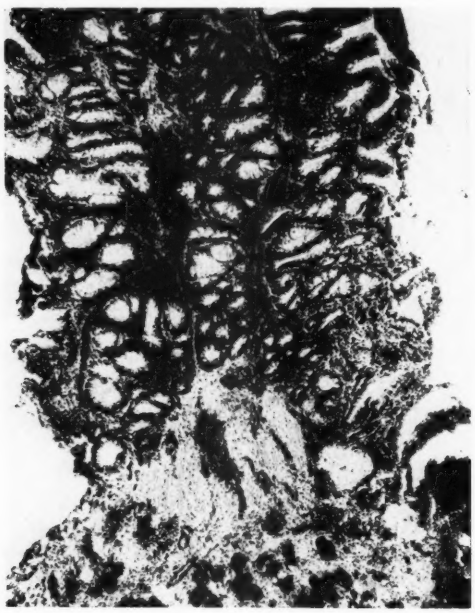

FIG. 9. Ulceration of the bladder type IV showing the relation of ulcer to the adenocarcinomatous tumor. Note that the calcific ova plaque and hyperplastic epithelium remain. ×70.

calcific plaque is formed as the process of degeneration and foreign body reaction are completed. When this calcification is forming the immediate ulceration of the epithelium is composed of a granulating surface. Ova that are vital may or may not be seen in the granulation tissue depending upon the site of deposition of the ova by the gravid female schistosome worm or whether antimony compounds have been instituted. When calcifying plaques are forming in the deep submucosal tissue and granulation tissue is present on the ulcer surface, a type II ulcer is present.

Since specific therapy is directed toward the living parasitic forms and does not rid the tissues of the dead or degenerating forms, the tissue reactions continue. As the calcified plaque becomes more intense and organized, the devitalized tissue overlying the plaque sloughs. At this stage little inflammatory cell reaction is seen provided that no new ova are in the process of degeneration. Attempts at healing the defect originate in the marginal epithelium and this stage is classified as type III. The attempts to repair the epithelial defect are usually not successful because of the poor or absent blood supply and loss of granulation tissue. The continued attempts of the marginal epithelium to bridge the gap lead to the polypoid lesions seen about the ulcers or may lead to transformation into a malignant process to establish a type IV ulcer. The relationship of metaplasia to malignancy in the bronchial epithelium has been discussed by Weller and the relationship and different types of malignant diseases of the bladder by Mostofi and Connery. Subsequent or repeated infestations may be superimposed on the bladder wall. The continued inflammation and chronic foreign body reaction along with hyperplasia of the epithelium lead to metaplasia. The metaplasia may be of the squamous cell pattern either focal or diffuse. It is usually accompanied by numerous simple glandular nests in the submucosa commonly called "cystitis cystica." Metaplasia when seen in these cysts is usually adenoid but squamous changes may also be observed.

Hemorrhage in the type III ulcer is often massive and usually required surgical resection to be controlled. The calcifying or calcified plaque interferes with contraction of the bladder wall and prevents the area from assuming a contracted state. The vessels seen in the resected specimens that are present beneath the ulcer crater are large and patent. It is seldom that the organized calcium plaque extends into the muscle coat. Although scattered calcified ova may be present in the interstitial tissues which separate the bundles of muscle cells, the organized plaque is separated by a layer of connective tissue from the muscle proper. In long standing cases or in those with a history of many years of schistosomal infections with treatment, the muscle layers show atrophy. This condition combined with the direct mechanical interference of the calci-

ied plaque are important factors in the surgical management of ulcers with gross hematuria. To assess the precise role played by the antimony compounds used in treatment of vesical schistosomiasis is impossible at this tage of the study. The compounds repeatedly employed may cause deposition of nonviable ova in the bladder wall and possibly enhance local reactions in the inflammatory sites of the bladder.

ISCUSSION

Although in this series of patients with ulcerations of the bladder associated with chistosomiasis there was a preponderance of males, this marked difference may not hold true as more cases are collected. Nevertheless, the occupation of the male in Egypt s mainly agricultural in type. Due to irrigational requirements and the intense schistosomal infestation, this occupation exposes he farmer to repeated infections by the ercaria. Although the incidence of urinary chistosomiasis may not differ greatly between the sexes, the density of infection or repeated infections may be important factors. Heavy manual efforts associated with primitive farming and other occupations may cause the clinical symptoms that demand medical attention.

The varying age at the time the patient seeks treatment apparently depends upon two factors: the intervals between primary infestation, and reinfection of significant severity to cause ulceration and the interference of the clinical symptoms and signs with gainful employment. On the other hand, complications of treated schistosomiasis that are severe enough to cause the patient to seek medical attention usually occur several years after treatment or from 12 to 16 years after initial infection, as pointed out in a previous paper (3).

Pain rather than hemorrhage becomes more prominent in the older lesions and reaches the point that only partial relief can be effected by subtotal resection of the bladder. These cases are associated with advanced fibrosis and a contracted bladder.

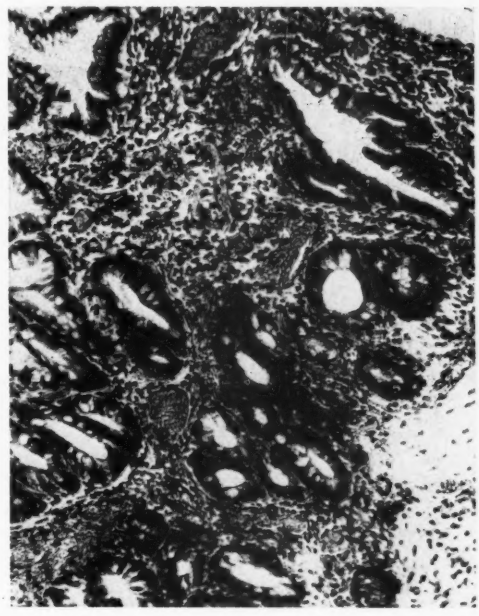

FIG. 10. Higher magnification of Figure 9 showing the atypical acini of the polypoid tumor in the margin of a type IV ulceration. ×202.

The site of ulceration in this series is similar to that previously recorded for the Hunner's ulcer of chronic interstitial cystitis. This is probably on the basis of the vascular arrangement of the bladder with the ulcer occurring in the end vessel regions. After diffuse fibrosis develops in the posterior wall and dome, as cited by Sorour, Hutchison, and Dew, little dilatation can compensate except in the trigone and part of urethra between internal and external sphincters.

In reviewing these cases of ulceration of the bladder, it was apparent that the treatment in popular use does not effect cure in the presence of the pathologic process. Thus was pointed out the need for further study of early and late cases, the attention of the urologic surgeon as well as the referring physician is called to the results of such a study. In a study of this type attempts can be made to establish a possible relationship of vesical schistosomiasis, a distinct parasitic entity, to a malignant process.

From this review of bladder ulcers, the histologic features indicate that the tissue reactions rather than the parasitic forms per se are the more important features of this clinical entity which bridge the gap to malignancy. Further, the mechanical alteration of bladder capacity is affected by fibrous tissue deposition and muscle atrophy rather than directly due to fusion of calcific forms of ova. Chemical substances or toxins as frequently referred to in the literature may be of little significance in advanced cases of long duration in which therapy has been administered.

Although important in types I and II ulcers, inflammation plays a decreasing role in types III and IV. Changes in the epithelium of the bladder are important features. Similar changes (e.g., epithelial and gland alterations) have been previously reported in a study of polypoid growths of the colon in schistosomiasis (3). These changes appear more marked in the bladder. This fact may be attributed either to specific features inherent to the urinary bladder epithelium or possibly to factors of urine composition. Nevertheless, the hyperplasia, metaplasia, and cystitis cystica, plus repeated attempts of healing constitute distinct differences between vesical and extravesical schistosomiasis. These differences may offer some explanation for the discrepancy in the incidence of malignant change in the bladder versus other organs.

The ulcer process appears to be the form of vesical schistosomiasis that may predispose to malignancy. At the same time, this form lends itself to surgical treatment. Although the control of hemorrhage and discomfort are the immediate aims, the possible prevention of malignant change or the excision of early carcinoma may be accomplished. Further studies are in progress in reference to clinically established carcinoma of the bladder and the relationship to ulceration in vesical schistosomiasis.

Classification of the ulcers was applied on the basis of the pathologic findings. Clinical correlation is as follows: In the type I ulcer coalescence of the numerous bilharziomas leads to gross ulceration. From the clinical findings, hematuria and painful frequent urination are prominent. Complete relief can be effected by surgical excision of the ulcers and painful employment can be resumed.

In a type II ulcer the process is further advanced and necrotic slough occurs with replacement by granulation tissue. Again as in the Type I ulcer the complaints and symptoms are almost exactly the same. Cystoscopy shows granulation tissue at the site of the ulcer. Hemorrhage and relief of symptoms can be obtained by partial cystectomy.

In a type III ulcer the prognosis is not as good as in types I and II because fibrosis and a contracted bladder are normally encountered. By partial cystectomy freedom from hemorrhage with its associated pain can be obtained and the type IV ulcer with malignancy may be prevented. Complete relief of all presenting complaints can rarely be accomplished. The value of partial cystectomy versus total cystectomy has not been determined over a sufficient period of time to allow any merited opinion.

Type IV ulcer cases require careful follow-up by cystoscopy for the possibility of neoplastic extension beyond the resected margins of the specimens. Further surgical resection may be indicated depending upon results of serial sectioning of the margins of the specimens, and repeated cystoscopic examinations. Adequate follow-up of this type of ulcer case has not been sufficiently long to evaluate treatment by partial cystectomy.

SUMMARY

A series of 33 cases of bladder ulceration associated with vesical schistosomiasis is reviewed. Detailed histopathologic examinations were performed in 31 of the cases. In these cases the pathologic processes initiated by primary infestation did not cease after adequate clinical treatment by antimony compounds. Hematuria, present in the majority of cases, constituted a surgical emergency. Partial resection of the bladder was

ound to be the treatment of choice. Pain ssociated with cases of long duration was ot completely relieved by partial resection f the urinary bladder.

The pathologic features are reviewed in letail and the ulcers classified into 4 types. The clinical features were correlated with he ulcer type. The cystoscopic findings indicated that malignant change in the bladder could not always be predicted without erial sectioning of the ulcers. Two cases of ulcer with malignant changes were found. The relationship to bladder malignancy as well as the pathogenesis are discussed. An additional study of malignant changes in urinary bladder is in progress and the relationship to ulceration due to schistosomal infestation will be explored.

It is concluded that latent ulcers of the bladder following treatment for vesical schistosomiasis constitute a clinical entity for which surgical resection is the only effective means of treatment.

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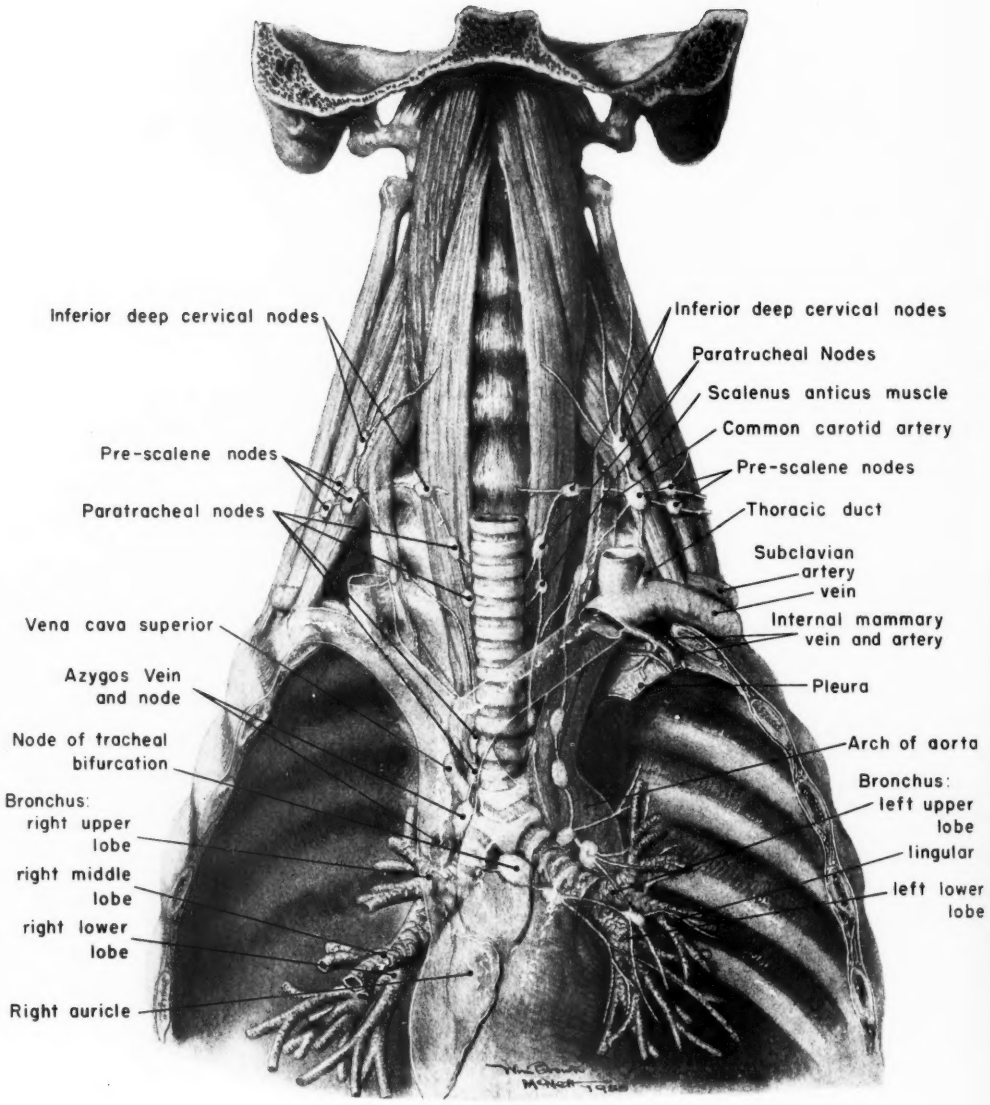

FIG. 1.

Prescalene and Deep Cervical Lymph Node Biopsy.—Richard G. Connar.

PRESCALENE AND DEEP CERVICAL LYMPH NODE BIOPSY

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THE PHYSICIAN who does chest surgery today is frequently confronted by a patient with an intrathoracic lesion in whom it becomes necessary to resort to thoracotomy in order to establish a diagnosis. It is well recognized that the mortality rate from a diagnostic thoracotomy in competent hands is quite low, but the patient will experience considerable pain and discomfort postoperatively. A simpler and less disabling procedure would be more desirable, especially, if it could establish the diagnosis and eliminate an unnecessary operation. In 1949, Daniels described a method of biopsy useful in diagnosing intrathoracic lesions when the diagnosis could not be established other than by a thoracotomy. In essence the procedure consisted of removing lymph nodes from the fat overlying the scalene muscle and then following the subclavian and internal jugular vein into the upper mediastinum, removing any nodes that were encountered. The operative approach was similar to that used for a phrenic nerve crush. Five cases were reported in which the biopsies were positive. There were 2 cases of Boeck's sarcoid, 1 case of silicosis, and 2 cases of carcinoma of the lung. One of the latter cases was found postoperatively, and Daniels commented that an unnecessary operation could have been avoided had the biopsy been done earlier.

Single cases of positive prescalene node biopsy were reported in 1951 by Weiss and associates (Boeck's sarcoid) and in 1952 by Johnson and MacCurdy (histoplasmosis). In 1953, Storey and Reynolds reported their experience with this procedure in a general discussion of biopsy techniques in the diagnosis of intrathoracic lesions. They referred to the operation as "resection of the deep cervical fat pad and contained nodes." Diagnosis was established in 5 cases. There were 3 cases of Hodgkin's disease, 1 case of Boeck's sarcoid, and 1 case of anaplastic carcinoma. Storey and Reynolds utilized the same operation as Daniels and referred to it as "a long used but little publicized method."

Shefts and his co-workers in 1953 were the first to publish an extensive experience with this procedure as a diagnostic method. They reported a positive tissue diagnosis in 67 (35.8 per cent) of 187 patients, 17 of whom had bilateral prescalene biopsies. The commonest diagnoses in this group were Boeck's sarcoid (38 patients) and carcinoma of the lung (13 patients). Other diagnoses established were tuberculosis, lymphosarcoma, Hodgkin's disease, and histoplasmosis.

In 1954, Harken and his associates published their experience with an extension of the original procedure described by Daniels. This was labeled a cervicomediastinal exploration, and they actually biopsied paratracheal nodes low in the neck and in the mediastinum. If a mass was encountered a lighted laryngoscope was inserted into the wound, and the mass was biopsied under direct vision. One hundred and forty-two cases were reported, and a positive histologic diagnosis was established in 45 cases or 31.7 per cent of the total. They emphasized that none of the patients had palpable supraclavicular nodes preoperatively. Carcinoma of the lung yielded a 39.8 per cent positive tissue diagnosis in 78 proved cases, and this was by far the commonest diagnosis in the series. Other proved diagnoses were Hodgkin's disease, Boeck's sarcoid, carcinoma of esophagus with metastases, granuloma compatible with tuberculosis, and plasmacytoma.

The present study was undertaken in order to evaluate: (1) the practical value of a prescalene biopsy in establishing the diagnosis in cases with previously undiagnosed intra-

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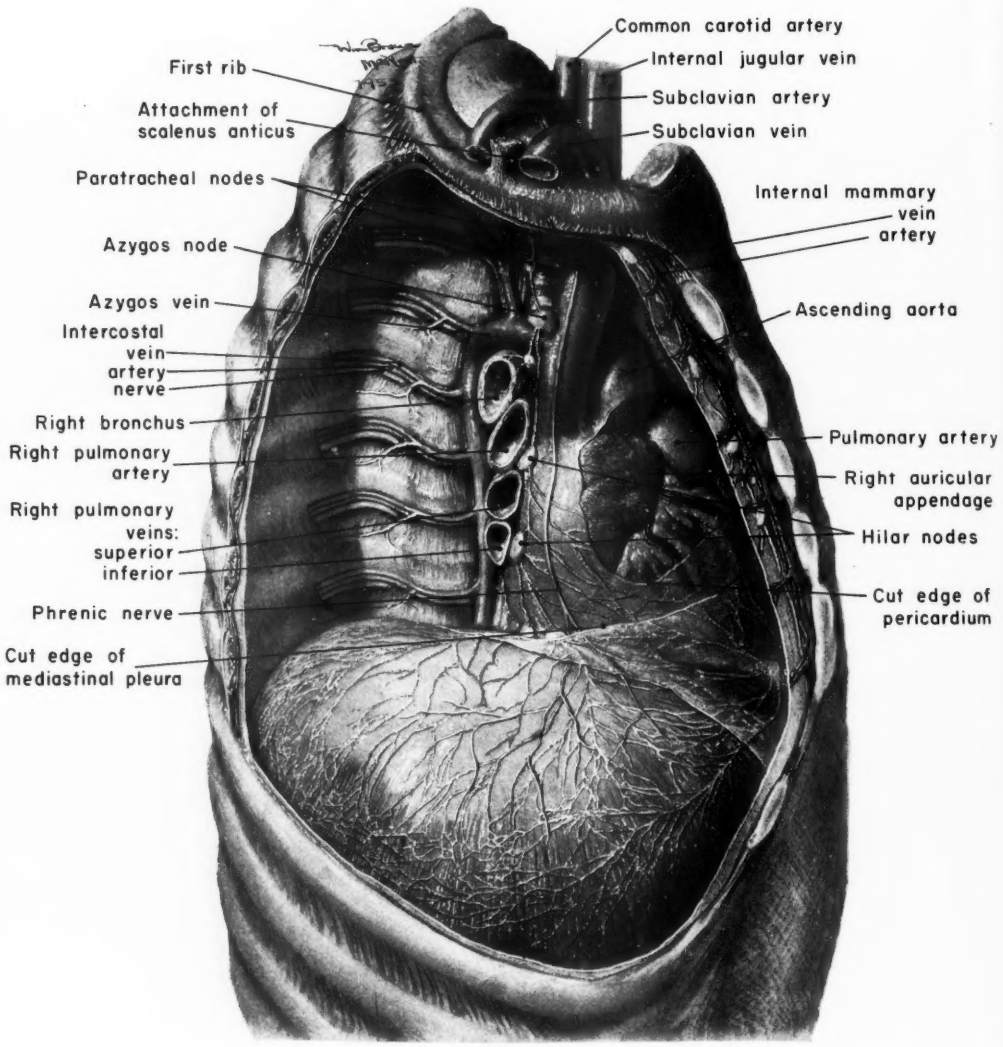


FIG. 2.

thoracic lesions, (2) the value of the procedure in preventing unnecessary thoracotomies in cases of carcinoma of the lung, i.e., when the malignancy has already spread beyond the limits of surgical excision.

LYMPHATIC DRAINAGE OF THE LUNG

It is surprising how incompletely the lymphatic drainage of the lung is described in the commonly used textbooks of anatomy. There is a common misconception that the lymphatic drainage of the left lung empties into the thoracic duct and that of the right lung empties into the right lymphatic duct. Rouviere's investigation of the lymphatic drainage of the lung in 200 preparations of fetuses, newborns, and children refutes this idea, as does Drinker's work on the dog.

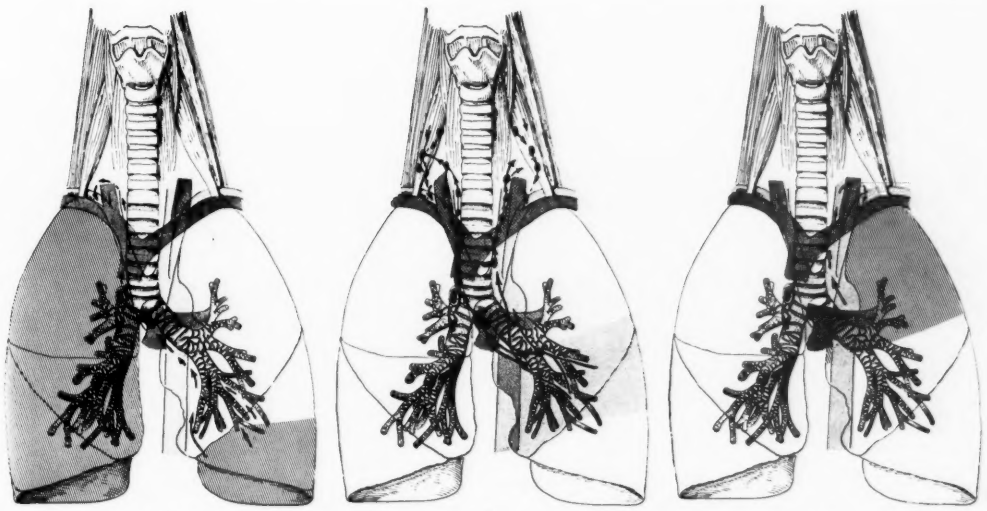


FIG. 3. Lymphatic drainage of (shaded areas): a, the right lung and the left lower lung field is to the right lymphatic duct; b, the left upper lung field is to the thoracic duct; c, the left midlung field is either to the thoracic duct or to the right lymphatic duct via the lymph nodes of the tracheal bifurcation.

The lymphatic drainage of the lung does not confine itself to a lobar pattern. The right lung in general presents a relatively simple pattern. Collecting channels for practically the entire lung empty into the right paratracheal nodes either directly or indirectly by way of the nodes of the tracheal bifurcation (Figs. 1 and 3a). There is consistently a rather large node just above the azygos vein which drains the upper lobe primarily. This in turn drains into the right paratracheal nodes (Fig. 2).

The left lung presents a more complex pattern (Figs. 1 and 3). It is conveniently divided into three regions of lymphatic drainage: superior, middle, and inferior. The superior lymphatic region (Fig. 3b) comprises the superior portion of the left upper lobe, the lymph collecting channels of which ultimately drain into the left paratracheal nodes. The middle lymphatic region (Fig. 3c) includes the inferior portion of the upper lobe as well as the superior and midportions of the lower lobe. The lymph collecting channels drain both superiorly into the left paratracheal nodes and inferiorly into the nodes of the tracheal bifurcation (Fig. 2), the latter ultimately emptying into the right paratracheal chain. The inferior lymphatic region (Fig. 3a) consists of the inferior part of the lower lobe, and its collecting channels empty into the nodes of tracheal bifurcation which drain into right paratracheal nodes.

The efferent vessels of the tracheobronchial chain join the efferent vessels of the internal mammary (Fig. 2) and anterior mediastinal nodes to form the bronchomediastinal trunk on either side. The right bronchomediastinal trunk may join the right lymphatic duct, and the left bronchomediastinal trunk the thoracic duct, or they may open independently into the junction of the internal jugular and subclavian veins. In the lower neck the inferior deep cervical nodes receive drainage from the higher paratracheal nodes via the superior deep cervical nodes and directly from the lower paratracheal nodes (Fig. 1). Drainage is hence to the right lymphatic duct on the right side and to the thoracic duct on the left side. If adhesions exist between the visceral and parietal pleura, lymphatic drain-

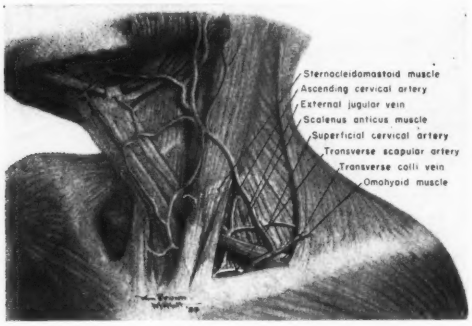


FIG. 4.

age of the lung may also occur by way of the chest wall, pericardium, and diaphragm.

TECHNIQUE

The technique is essentially that originally described by Daniels. The patient is placed on the operating table in the supine position with the shoulder of the operative side elevated about 15 degrees and the head rotated to the opposite side. After infiltrating the skin and subcutaneous tissues with 1 per cent xylocaine or procaine, a 5 to 7 centimeter skin incision is made parallel to the natural creases of the neck approximately 2 centimeters cephalad to the head of the clavicle (Fig. 5). The midpoint of the incision should be just lateral to the lateral border of the sternocleidomastoid muscle. The external jugular vein is divided if necessary. The sternocleidomastoid muscle is either partially divided or mobilized and retracted medially. The omohyoid muscle may course diagonally across the superior aspect of the field, and this structure may either be divided or retracted (Fig. 4). Up to this point the technique is the same as that used for exposure of the phrenic nerve. The fat overlying the scalenus anticus muscle is readily exposed (Fig. 5). By using alternate sharp and blunt dissection the fat is mobilized medially to the internal jugular vein, inferiorly to the junction of the jugular and subclavian veins, laterally to the brachial plexus, and superiorly to the upper limits of the incision. It is our practice to clamp, divide, and ligate most of this tissue because of the numerous lymphatic channels in this region. If suspicious nodes are felt in the prescalene fat, a frozen section may eliminate the necessity of a more extensive dissection. As the scalenus anticus muscle is exposed, the transverse cervical vessels and branches of the thyrocervical trunk may be encountered (Figs. 4 and 5). These vessels may be ligated in order to facilitate removal of the prescalene fat. One should avoid damaging or dividing the phrenic nerve. When operating on the left side the thoracic duct may be divided if caution is not exercised. Following the procedure as described, one actually enters the superior mediastinum at the junction of the internal jugular and subclavian veins. The paratracheal region can be palpated for any enlarged lymph nodes, which are biopsied if palpable. The wound is closed in anatomic layers without drainage.

The excised tissue should be palpated carefully by the surgeon and the pathologist before it is fixed. In this manner lymph nodes may be detected and blocks taken through suspicious areas.

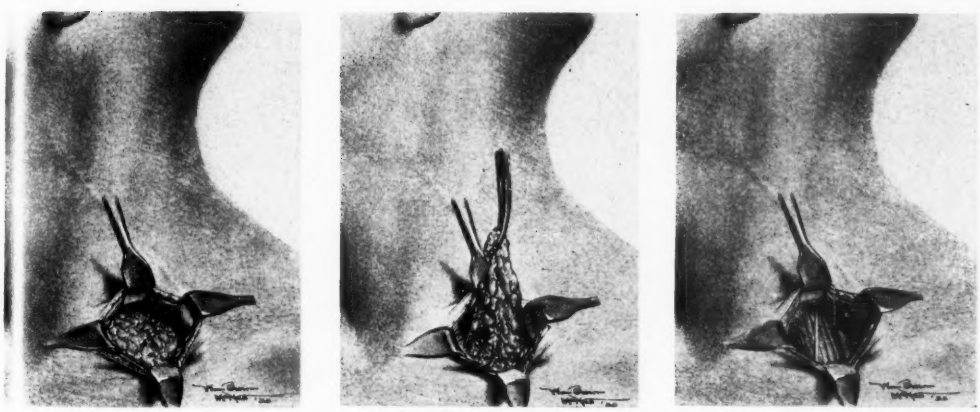
TABLE I.—FIFTY CONSECUTIVE CASES PRESCALENE LYMPH NODE BIOPSY

Diagnosis	*No. of cases*
Carcinoma of the lung	29
Inflammatory disease	9
Boeck's sarcoid	5
Tuberculosis	3
Hodgkin's disease	1
Aneurysm of ascending aorta	1
Aneurysm of pulmonary artery	1
Pulmonary fibrosis	1
Total	50

RESULTS

The group under study consists of 50 consecutive cases of previously undiagnosed intrathoracic lesions seen originally, or in consultation by the Thoracic Surgery Section during the 9 month period from March 1954 to January 1955. It was customary for the patient to be bronchoscoped, following which a prescalene and deep cervical lymph node biopsy was done.

Of the total 50 cases, there were 29 cases of carcinoma of the lung, 9 cases of inflam-



a b c

FIG. 5. Operation: a, prescalene fat exposed; b, prescalene fat and contained lymph nodes being removed; c, exposure of scalenus anticus muscle and phrenic nerve after removal of prescalene fat and lymph nodes.

inflammatory disease, 5 cases of Boeck's sarcoid, 3 cases of tuberculosis, and single cases of Hodgkin's disease, aneurysm of the ascending aorta, aneurysm of the pulmonary artery, and pulmonary fibrosis (Table I). A positive tissue diagnosis was made in 25 of the 29 cases of carcinoma of the lung either by prescalene biopsy, bronchoscopy, thoracotomy, or autopsy. Of the remaining 4 cases, a clinical diagnosis was established in 2 by thoracotomy, although adequate biopsy material was not obtained. In the third case there were distant metastases present, and in the fourth case the patient has paralysis of the recurrent laryngeal nerve and has deteriorated. Both of the thoracotomized patients have also deteriorated. A diagnosis of the inflammatory disease was verified by subsequent regression of symptoms and clearing of the chest by x-ray examination. In the cases of the Boeck's sarcoid the clinical course of the patients has been compatible with this diagnosis. The diagnosis of tuberculosis was established either by thoracotomy or positive culture. The diagnosis of aneurysm of the pulmonary artery was established by angiocardiography and the aneurysm of the ascending aorta was discovered at thoracotomy.

A diagnosis was established by prescalene and deep cervical lymph node biopsy in 14 (28 per cent) of the 50 cases (Figs. 6 through 10). If only the disease processes in which it is possible to establish a specific diagnosis by lymph node biopsy are considered, the incidence of positive biopsy is 36.8 per cent (Table II). In the 29 cases of carcinoma of the lung there was a positive prescalene biopsy in 9 cases, an incidence of 31 per cent. Small supraclavicular lymph nodes were palpable preoperatively in 1 (biopsy positive) of the 5 cases of Boeck's sarcoid, in the single case of Hodgkin's disease, and in 6 patients with carcinoma of the lung. Of the latter group only 3 had positive prescalene biopsies (Table III).

The distribution of the primary lesions in patients with metastatic carcinoma in prescalene and deep cervical lymph nodes is shown on Table IV. Since lymphatic drainage does not follow lobar pattern (Fig. 3), the lesions were classified either in the upper, middle, or lower lung field depending on the appearance of the x-ray film (poste-

TABLE II.—POSSIBLE DIAGNOSIS BY PRESCALENE LYMPH NODE BIOPSY

Final diagnosis	*Total cases*	*Positive biopsy*	*Per cent of total*
Carcinoma of the lung	29	9	31
Boeck's sarcoid	5	4	80
Tuberculosis	3	0	0
Hodgkin's disease	1	1	100
Total	38	14	36.8

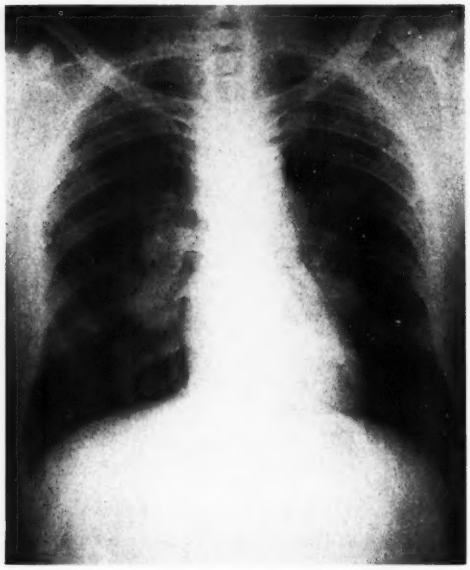


FIG. 6. Asymptomatic 27 year old colored male. No palpable supraclavicular lymph nodes and bronchoscopy negative; blood chemistries, roentgenograms of hands normal. Boeck's sarcoid diagnosed by prescalene, deep cervical lymph node biopsy (right). Follow-up 16 months.

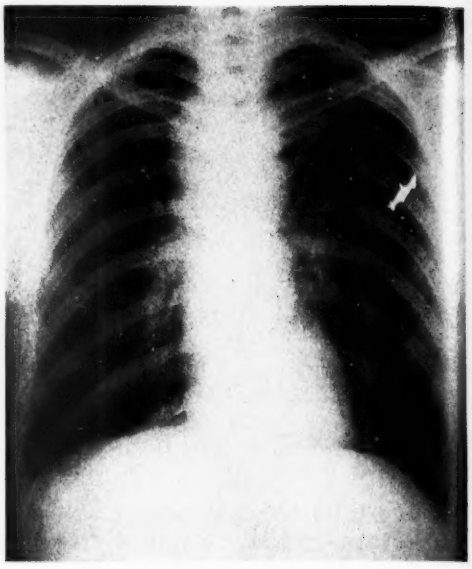


FIG. 7. Thirty-four year old white male. Small shotty supraclavicular lymph nodes present bilaterally. Bronchoscopic examination negative. Hodgkin's disease diagnosed by prescalene and deep cervical lymph node biopsy (right).

rior-anterior view) of the chest. In several cases localization was difficult because of the size of the lesion, and in 1 case the pleural effusion was so massive that the underlying lesion could not be localized. Although this is a relatively small series, it is interesting to note that there are no positive prescalene biopsies in lower lung field carcinomas. The localization of the primary lesion in all of the patients with carcinoma of the lung is shown in Table V.

A positive tissue diagnosis of carcinoma was obtained by bronchoscopic biopsy in 9 of the 29 cases of carcinoma of the lung (Table VI). This is an incidence of 31 per cent which is identical with the incidence of positive prescalene biopsy. There were 6 additional cases in which there was indirect evidence of carcinoma by bronchoscopy, but tissue diagnosis could not be made. Bronchoscopy was not done in 1 case because the patient was too ill (subsequently died). In another case the prescalene biopsy was done first and found to be positive. The case was considered to be inoperable, and the patient was not bronchoscoped.

TABLE III.—CARCINOMA OF THE LUNG IN 29 CASES

	Palpable	*Not palpable*	*Total*
Supraclavicular lymph nodes	6	23	29
Prescalene lymph node biopsy			
Positive	3	6	9
Negative	3	17	20

The cases of carcinoma of the lung in which a tissue diagnosis was made are listed in Table VII. Undifferentiated carcinoma was commonest in the group in which metastatic carcinoma was found in the prescalene and deep cervical lymph nodes. Squamous cell carcinoma was commonest in the group with negative prescalene biopsies.

Prescalene biopsies were considered inadequate if there were less than 4 lymph nodes in the removed tissue and no anthracotic pigment seen microscopically. This is an arbitrary criteria established by the author and the pathologist. Eight biopsies were

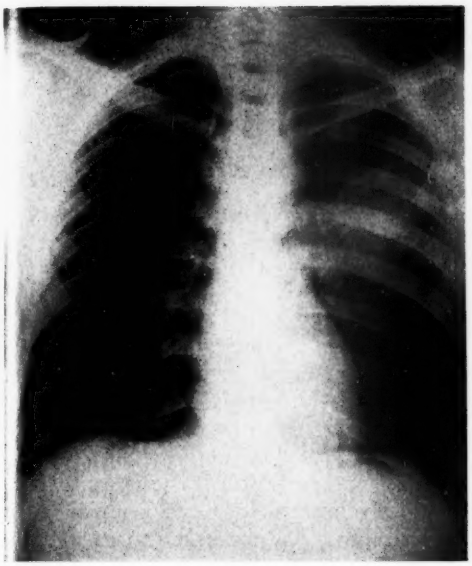


FIG. 8. Twenty-four year old colored male. No palpable supraclavicular lymph nodes. Bronchoscopic examination negative. Metastatic undifferentiated carcinoma found in prescalene and deep cervical lymph node biopsy (left).

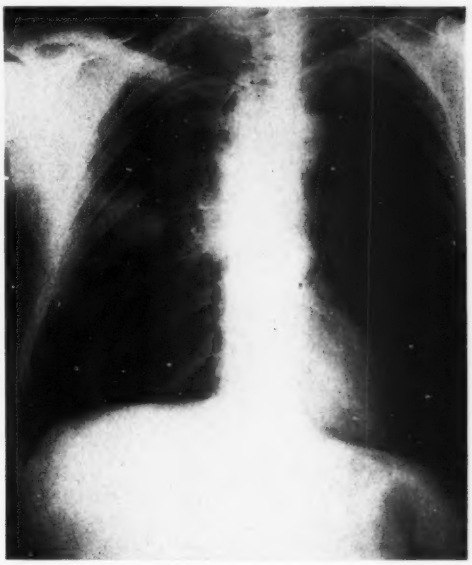


FIG. 9. Sixty-four year old white male. Single small palpable supraclavicular lymph node on right. Bronchoscopy negative. Metastatic squamous cell carcinoma found in prescalene and deep cervical lymph node biopsy (right).

considered inadequate. Five of the 8 occurred in cases of carcinoma of the lung, 2 occurred in cases of pulmonary tuberculosis, and 1 occurred in a case of chronic pneumonitis.

DISCUSSION

Prior to Harken's article very little attention had been given to the lymphatic drainage of the lung. Neither Daniels nor Storey mentioned which side should be biopsied. Shefts and his associates selected the right side in cases of bilateral involvement, for they thought it was a safer procedure. They proceeded to say: "It is obvious, however, that usually and quite properly the scalene nodes on the same side as the principal intrathoracic involvement would be the one chosen for biopsy. When there is no pulmonary lesion and the enlargement of the mediastinum is equal bilaterally, it is probable that the highest percentage of positive nodes would be found on the left." Although there were 35 per cent positive findings in cases biopsied on the right versus 30 per cent on the left, they did not think this was statistically significant. Of 17 bilateral biopsy cases, only 2 were positive on both sides. One was a case of Boeck's sarcoid, and the other was a case of left lower lobe carcinoma with a mediastinal mass.

Shefts' impression of the lymphatic drainage of the lung was shared by the author at the outset of this study as a result of a statement in *Gray's Anatomy*. "The thoracic duct is the common trunk of all the lymphatic vessels of the body, excepting those on the right side of the head, neck, and thorax, and right upper extremity, the right lung,

TABLE IV.—METASTATIC CARCINOMA IN PRESCALENE LYMPH NODES (9 CASES)

Site of primary lesion	*Right side*	*Left side*
Upper lung field	3	3
Middle lung field	2	0
Lower lung field	0	0
Massive pleural effusion	0	1
Total	5	4

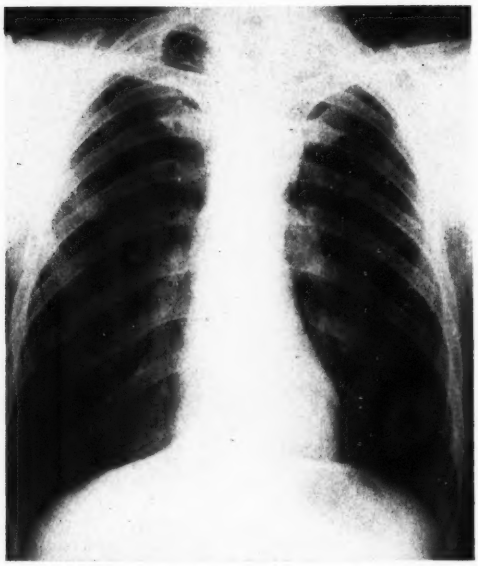


FIG. 10. Fifty-nine year old white male with Pancoast's syndrome, left. No palpable supraclavicular lymph nodes. Metastatic adenocarcinoma found in prescalene and deep cervical lymph node biopsy (left).

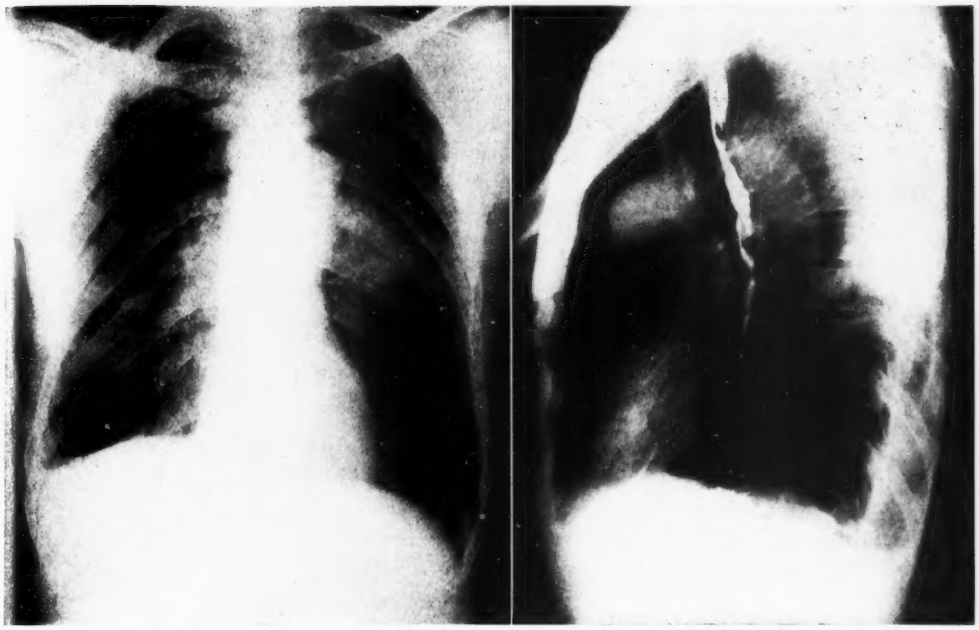
the right side of the heart, and the convex surface of the liver." Although a number of the anatomy textbooks give a very adequate discussion of mediastinal drainage, there is comparatively little concerning the lung. One is left with the impression that the left lung is drained by the left bronchomediastinal trunk into the thoracic duct. Harken and his associates refer to Rouviere's description of the lymphatic drainage of the lung and to Drinker's work on the dog as the basis for their selection of the side for biopsy. They employ bilateral biopsy in cases with left lower lung lesions. Otherwise, the left side is biopsied for left upper lung lesions and the right side for right upper and right lower lung lesions. The author agrees with this principle with the exception that left mid-lung field lesions should also be biopsied on both sides (Fig. 11). In patients with bilateral lesions or mediastinal mass and absent palpable supraclavicular nodes, biopsy is preferable on the right. Not only is one less likely to damage the thoracic duct as mentioned by Shefts and his co-workers, but there is theoretically a greater chance of positive biopsy. If nodes are palpable, there is no problem as to which side to biopsy.

TABLE V.—CARCINOMA OF THE LUNG IN 29 CASES

Site of primary lesion	*Right side*	*Left side*
Upper lung field	9	7
Middle lung field	1	1
Lower lung field	4	4
Massive pleural effusion	1	2
Total	15	14

Although Harken makes a point that his operation entails entering the mediastinum, it is very likely from the description of their operative techniques that Daniels, Storey and Reynolds, and Shefts and his associates all entered the mediastinum. Their dissection was not as deep or as extensive, however, as Harken advocates. The author has observed Harken doing a cervicomediastinal dissection and has done the procedure on a number of patients himself prior to this study. It was concluded that a cervicomediastinal exploration was potentially a more hazardous procedure and added to the discomfort of the patient if done under local anesthesia. Although the incidence of positive biopsy in cases of carcinoma of the lung may be slightly higher with a more extensive operation (31 per cent in our series versus 39.8 per cent in Harken's series), it is the author's feeling that this does not outweigh its disadvantages. As mentioned previously, it is our policy to dissect into the mediastinum just beyond the junction of the internal jugular and subclavian veins and palpate for paratracheal nodes. It is quite important when one does a so-called "prescalene biopsy" that dissection be carried medially to include the inferior deep cervical lymph nodes. On 2 occasions these nodes were positive when the "prescalene lymph nodes" were negative. There was also a case in which lateral extension of the prescalene fat over the brachial plexus contained a lymph node with metastatic carcinoma from the lung while all of the remaining nodes in the specimen were negative.

One of the problems encountered in this series was inadequate tissue removal at the



a b

FIG. 11. Sixty year old colored male (pleurisy and fractured ribs on right 20 years ago). No palpable supraclavicular lymph nodes. Bronchoscopy negative. Left prescalene and deep cervical lymph node biopsy revealed normal lymph nodes. Metastatic undifferentiated carcinoma found in right prescalene and deep cervical lymph node biopsy. (Case subsequent to original 50 cases.) a, Posteroanterior view reveals midlung field and mediastinal masses. b, Lateral x-ray film with barium swallow reveals compression of esophagus by mediastinal masses and a lesion in the superior segment of the left lower lobe.

time of biopsy. Contrary to opinion expressed by others, the author believes that a prescalene lymph node biopsy is not a simple procedure when done properly, and it takes as much time as the average appendectomy. The majority of our biopsies were done by surgical residents. In 2 instances it was necessary to rebiopsy the patient as there was nothing but fat in the specimen. The rebiopsy specimen in each case contained 10 to 14 lymph nodes. At the termination of the study all specimens were re-examined microscopically, and it is of interest that 5 of the 8 inadequate biopsies were in patients with carcinoma of the lung. In 3 of the 5 cases there were only 2 lymph nodes in the specimen. Anthracotic pigment was invariably seen in specimens containing a large number of lymph nodes. When a specimen contained only 2 to 3 lymph nodes and no anthracotic pigment, it was thought that there was not only inadequate lymphoid tissue in the biopsy, but it also was not in the path of the lymphatic drainage of the lung. One must be careful in looking for anthracotic pigment, however, for it may be confused with formalin pigment. The latter may be avoided by using a different fixative. The author has heard several surgeons belittle the prescalene biopsy because of their low inci-

TABLE VI.—CARCINOMA OF THE LUNG

	Prescalene biopsy	
Bronchoscopic diagnosis	*Positive*	*Negative*
Positive (dir.)	1	8
Positive (ind.)	2	4
Negative	5	6
Unsatisfactory	0	1
Not done	1	1
Total cases	9	20

TABLE VII.—TISSUE DIAGNOSIS ESTABLISHED IN 25 OF 29 CASES OF CARCINOMA OF THE LUNG

Prescalene biopsy	*Positive*	*Negative*
Squamous cell carcinoma	2	10
Adenocarcinoma	2	3
Undifferentiated carcinoma	5	3
Total	9	16

dence of positive results. Since this study, I cannot help but wonder how frequently inadequate tissue is removed.

In the entire series there was 1 complication. A large lymphatic channel was transected on the left side. This was most likely the thoracic duct, although it was not recognized at the time of operation. Lymph drainage was quite profuse initially, but it completely subsided 2 weeks later following x-ray therapy. Complications encountered by others have been pneumothorax, hemorrhage, thoracic duct injury, and Horner's syndrome. The incidence has been extremely low.

The high incidence of positive biopsy in cases of Boeck's sarcoid has been experienced by others. In 1 of our cases, a lacrimal gland biopsy was normal while the prescalene biopsy was compatible with Boeck's sarcoid. In none of the 4 patients with positive biopsies were there changes in the roentgenograms of the hands. A diagnosis of Boeck's sarcoid had been made elsewhere a year previously in the 1 case of a negative prescalene biopsy. Three months later the patient's chest film appeared normal.

In the patients with carcinoma of the lung, the most impressive finding is the incidence of metastatic carcinoma in the prescalene and deep cervical lymph nodes. This has been reported by others. When compared with bronchoscopy the incidence of positive biopsy was exactly the same. There were 2 cases, however, in which tumors could be seen in the upper lobe bronchus using the Broyles right angle lens, but biopsy was not feasible. As might be predicted undifferentiated carcinoma was the most commonly encountered malignant condition in the prescalene and deep cervical lymph node biopsies (Table VII). In 1 case a positive biopsy was also obtained by bronchoscopy.

Once a malignant lesion of the lung has metastasized to the prescalene and deep cervical lymph nodes, it is hardly conceivable that a cure can be accomplished by pneumonectomy, no matter how radical the hilar and mediastinal lymph node dissection. This may not be true if only the biopsy from deep in the mediastinum is positive. Thus, it is the author's belief that all patients with suspected carcinoma of the lung should have a bronchoscopic examination followed by a prescalene and deep cervical lymph node biopsy. If the prescalene biopsy is positive, exploration should be reserved for palliation in cases of major hemorrhage or infection.

SUMMARY

Experience is reviewed with prescalene and deep cervical lymph node biopsy in 50 consecutive cases with previously undiagnosed intrathoracic lesions. The procedure is evaluated both as a diagnostic method and as a means of avoiding pulmonary resection when a carcinoma of the lung has spread beyond the limits of surgical excision. The lymphatic drainage of the lung and the operative technique are described. The selection of the proper side for biopsy is discussed. Positive tissue diagnosis was established by prescalene and deep cervical lymph node biopsy in 9 cases of carcinoma of the lung, 4 cases of Boeck's sarcoid, and 1 case of Hodgkin's disease. The incidence of a positive tissue diagnosis was the same (31 per cent) as by bronchoscopic biopsy. Undifferentiated carcinoma was the most commonly encountered malignant disease in the prescalene and deep cervical lymph node biopsies. There was a high incidence of positive biopsy in cases of Boeck's sarcoid.

If the prescalene and deep cervical lymph node biopsy is positive in the case of carcinoma of the lung, exploration should be reserved as palliation for major hemorrhage or infection.

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ROLE OF ADRENALS AND OVARIES IN RESISTANCE TO MASSIVE DOSES OF ESTRADIOL

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EARLIER OBSERVATIONS have shown that both the adrenals and the ovaries play important rôles in determining resistance against estradiol intoxication. In rats treated with the same dose of estradiol the mortality rate was lower and the thymus involution more pronounced among simply adrenalectomized than among adrenalectomized-ovariectomized animals (1).

In all the surviving, merely adrenalectomized females of these earlier experiments, the corpora lutea underwent considerable hypertrophy under the influence of estradiol; hence, the question arose whether progesterone secretion might be involved in the development of the marked thymus atrophy and the concurrent increased resistance against estradiol intoxication.

It is the object of this communication to report upon investigations designed to clarify these points. At the same time, we wished to re-examine the possible participation of corticoids in the inhibition of growth and inflammation by ovarian hormones, because these changes—like systemic resistance and thymus atrophy after adrenalectomy—are rather characteristic of glucocorticoids.

MATERIALS AND TECHNIQUES

All our experiments were performed on female Sprague-Dawley rats, subdivided into groups of 10 animals each and having a mean body weight of between 158 and 162 grams. The maximum individual body weight range permitted within any one group was 10 grams below or above the mean.

All gland extirpations were performed under ether anesthesia. For the sake of uniformity, the adrenals and ovaries were removed through the lumbar route, essentially the same type of incision and technique being used in all cases. In order to obtain fully comparable conditions as regards trauma, the intact controls were subjected to a sham adrenalectomy and ovariectomy. This procedure consisted in approaching the adrenals and ovaries through the lumbar route, as usual, and then merely separating them from adjacent tissue, great care being taken not to interfere with their blood supply.

All hormones were administered in the form of microcrystal suspensions daily, subcutaneously, in 0.2 milliliter of water, unless specifically otherwise indicated in the text. Cortisol[1] acetate (COLA) and desoxycorticosterone acetate (DOCA), estradiol, and progesterone were the steroids employed in this investigation.

For the quantitative assessment of inflammation "granuloma pouches" were prepared in all animals, according to the technique described elsewhere (4). In essence, this procedure is carried out by injecting 25 milliliters of air, under the shaved dorsal skin, this being immediately followed by the introduction of 0.5 milliliter of a 1 per cent croton oil solution (in corn oil) into the air cell thus created. In all the experiments reported in this communication, the granuloma pouches were made on the first day, but adrenalectomies, gonadectomies, and

Supported by a Consolidated Grant from the National Research Council of Canada.

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[1]In agreement with the suggestion made by Shoppee, the term cortisol is used here in preference to hydrocortisone, since it eliminates confusion with 4, 5-dihydrocortisone and obviates the possible implication that hydrocortisone is to be regarded primarily as a mere derivative of cortisone.

TABLE I.—INTERACTIONS BETWEEN ESTRADIOL AND CORTICOIDS (FIRST EXPERIMENT)

Group	Treatment			Final body weight, gm.	Weight gain, per cent	Exudate, ml.	Thymus, mgm.	Spleen, mgm.	Lymph nodes, mgm.	Mortality, per cent
	Adrenal	Ovary	Hormone*							
I	Adr-X†	Intact	—	154 ± 4.0	−3.7	16.0 ± 1.4	366 ± 32.2	718 ± 46.3	‡	0
II	Adr-X	Intact	Estradiol	—	—	—	—	—	—	100
III	Adr-X	Intact	COLA	150 ± 3.5	−7.4	8.6 ± 1.0	157 ± 13.1	467 ± 35.2	15.8 ± 1.7	0
IV	Adr-X	Intact	Estradiol + COLA	111 ± 3.9	−30.6	2.1 ± 1.0	29 ± 3.3	‡	13.8 ± 2.3	10
V	Adr-X	Intact	DOCA	168 ± 3.6	+3.7	18.7 ± 2.8	374 ± 17.7	1050 ± 87.7	‡	0
VI	Adr-X	Intact	Estradiol + DOCA	142 ± 5.5	−9.5	10.0 ± 1.6	118 ± 14.9	469 ± 49.0	33.9 ± 3.8	70
VII	Adr-X	Ov-X	DOCA	175 ± 4.6	−10.0	16.0 ± 1.8	456 ± 37.7	881 ± 79.9	31.9 ± 1.8	0
VIII	Adr-X	Ov-X	Estradiol + DOCA	134 ± 10.5	−16.2	7.0 ± 2.0	173 ± 8.9	412 ± 16.6	25.8 ± 1.8	70

*In all groups the daily dose of the steroids listed in this column was the same, namely: estradiol 200 μgm., COLA 400 μgm., and DOCA 100 μgm.
†Since these animals received no corticoid therapy, they had to be given 1% NaCl as a drinking fluid for life-maintenance.
‡Specimens accidently lost in this group.

treatment with the various hormone preparations were postponed until 48 hours later to permit the establishment of a granulomatous wall and recovery from the trauma incidental to the production of the granuloma pouch.

Throughout the experiments all the animals were maintained exclusively on a Purina Fox Chow diet and received water or 1 per cent sodium chloride as drinking fluid, as indicated in our tables.

The formation of exudate was followed daily by transillumination of the air sacs with an electric flashlight, and all the animals were killed 12 days after preparing the granuloma pouch (except experiment 4, which was terminated on the ninth day, for reasons which we will explain later).

Immediately after autopsy, the accumulated exudate was accurately measured by aspiration into a graduated syringe, the final body weight (minus exudate) was determined and the organs listed in the tables were dissected, fixed in formalin, and, 24 hours later, weighed.

The mean values (with their standard error) of all these measurements are recorded in our tables.

EXPERIMENTAL OBSERVATIONS

Since all our principal findings are summarized in the form of tables, it will suffice merely to comment on a few salient points.

First experiment. As outlined in Table I, the first experiment consisted of a study of the effects of estradiol alone or in combination with corticoids in groups of merely adrenalectomized and 2 groups of adrenalectomized-ovariectomized rats. The main purpose of this investigation was to determine what maintains life after adrenalectomy in estradiol-overdosed animals, and whether, depending upon the type of corticoid substitution therapy offered, the actions of estradiol upon body weight, inflammation, and the lymphatic organs can be dissociated from each other. In order to assess the rôle of the adrenals and ovaries in resistance against estradiol, it is manifestly of interest to determine whether the individual actions of this folliculoid hormone upon its various targets are always proportionate to each other, or whether more selective organotropic effects can be obtained by suitable conjoint therapy with other steroids.

The high dose of 200 micrograms per day of estradiol employed in this experiment resulted in 100 per cent mortality among the adrenalectomized rats maintained on sodium chloride alone (group II). DOCA reduced this to 70 per cent and COLA to 10.

As judged by the final body weight and the weight gain, estradiol greatly augmented the catabolic effect of COLA (compare groups III and IV), but it produced a much less marked decrease below the initial body weight in the adrenalectomized (compare groups V and VI) or adrenalectomized-ovariectomized (compare groups VII and VIII) animals treated with DOCA.

TABLE II.—INTERACTIONS BETWEEN ESTRADIOL AND CORTICOIDS (SECOND EXPERIMENT)

Group	Treatment			Final body weight, gm.	Weight gain, per cent	Exudate, ml.	Thymus, mgm.	Spleen, mgm.	Lymph nodes, mgm.	Mortality, per cent
	Adrenal	Ovary	Hormone*							
I	Intact†	Intact†	—	180 ± 3.1	+11.1	13 ± 1.6	211 ± 20.6	849 ± 86.2	36.0 ± 1.7	0
II	Intact†	Intact†	Estradiol	162 ± 4.0	+2.5	4 ± 0.8	44 ± 5.4	414 ± 23.3	32.5 ± 2.7	0
III	Adr-X	Ov-X	COLA	162 ± 3.2	+3.8	5 ± 1.9	167 ± 12.4	461 ± 33.8	32.0 ± 2.2	0
IV	Adr-X	Ov-X	Estradiol + COLA	110 ± 3.2	−30.3	1 ± 0.3	38 ± 5.6	174 ± 13.7	10.0 ± 0.7	20
V	Adr-X	Ov-X	DOCA	189 ± 2.1	+20.2	15 ± 1.6	499 ± 23.5	1074 ± 30.7	32.2 ± 8.4	0
VI	Adr-X	Ov-X	Estradiol + DOCA	138 ± 3.3	−12.6	11 ± 1.6	168 ± 14.0	471 ± 36.6	29.4 ± 1.8	100
VII	Adr-X	Ov-X	COLA + DOCA	172 ± 2.7	+9.5	14 ± 2.6	238 ± 29.3	776 ± 22.4	21.7 ± 2.9	0
VIII	Adr-X	Ov-X	Estradiol + COLA + DOCA	145 ± 3.0	−9.6	10 ± 2.2	113 ± 11.3	424 ± 39.4	22.3 ± 1.4	0

*In all groups the daily dose of the steroids listed in this column was the same, namely: estradiol 200 μgm., COLA 400 μgm., DOCA 100 μgm.
†Pseudoadrenalectomies and pseudo-ovariectomies.

In all instances, estradiol exerted some antiphlogistic effect, but only in the rats maintained on COLA did this result in a virtually complete suppression of exudation (group IV).

It should be emphasized that, in the present experiment, we used massive doses of estradiol, since our principal object was to study the effect of other steroids upon the lethal actions of this folliculoid. In earlier investigations (1), in which smaller, more physiologic doses of estradiol were used, the hormone inhibited exudation only in adrenalectomized rats maintained on COLA and not in those treated with DOCA. It is quite probable that the high doses of estradiol used here acted rather nonspecifically, by interfering with the appetite and the general well-being of our experimental animals.

The intense synergism between cortisol and estradiol is particularly manifest as regards the lymphatic tissues. The thymus and the lymph nodes were maximally atrophic only in the estradiol-treated adrenalectomized animals maintained on COLA (group IV).

In this respect, an interesting dissociation in the individual effects of estradiol was noted. The thymus of the merely adrenalectomized (DOCA + estradiol-treated) rats (group VI) was significantly more atrophic than that of the similarly treated adrenalectomized and ovariectomized animals (group VIII). This is not noteworthy because the inhibitory effects of estradiol upon body weight, exudate formation, the spleen, and the lymph nodes were not more pronounced (indeed, they were less, but not significantly less, intense) than in the former group.

Another interesting dissociation of effects is discernible when we compare mortality rates with thymus involution. For instance, the mortality rate after estradiol intoxication is much greater in DOCA-treated adrenalectomized rats (group VI) than in those kept on COLA (group IV), yet the thymus involution is far more intense in the latter group.

Second experiment. For comparative purposes, a second experiment was then performed under essentially identical conditions on estradiol-treated, simultaneously adrenalectomized and ovariectomized rats given substitution therapy with COLA or DOCA.

In comparing the first with this second experiment, the most striking finding is that estradiol proves to be much more toxic to adrenalectomized-ovariectomized animals. This increased toxicity of estradiol in the absence of both steroid-producing glands is noted, irrespective of whether the animals are maintained on COLA (group IV) or DOCA (group VI). On the other hand, even ovariectomized and adrenalectomized rats can withstand these high doses of estradiol without any mortality if they are given conjoint treatment with both types of corticoids (group VIII).

TABLE III.—INTERACTIONS BETWEEN ESTRADIOL AND CORTICOIDS (THIRD EXPERIMENT)

Group	Treatment			Final body weight, gm.	Weight gain, per cent	Exudate, ml.	Thymus, mgm.	Spleen, mgm.	Mortality, per cent
	Adrenal	Ovary	Hormone*						
I	Adr-X	Ov-X	—	144.1 ± 3.6	−9.9	5.2 ± 0.6	293.2 ± 23.1	378.8 ± 22.1	30
II	Adr-X	Ov-X	Estradiol	—	—	—	—	—	100
II	Adr-X	Ov-X	Progesterone	173.9 ± 3.0	+8.0	12.3 ± 1.4	303.8 ± 26.2	640.8 ± 28.7	0
IV	Adr-X	Ov-X	Estradiol + progesterone	130.6 ± 5.6	−18.3	5.6 ± 0.7	63.6 ± 6.4	364.0 ± 56.7	70
V	Adr-X†	Ov-X	Estradiol	126.0 ± 3.1	−23.6	5.0 ± 1.4	122.6 ± 9.2	310.6 ± 24.4	100

*In all groups the daily dose of the steroids listed in this column was the same, namely: estradiol 40 μgm., progesterone 5,000 μgm.
†Since these animals received no corticoid therapy, they had to be given 1 per cent NaCl as a drinking fluid for life maintenance.

The body weight is least markedly depressed by estradiol in intact rats (group II) and most markedly in adrenalectomized-ovariectomized animals maintained with COLA alone (group IV). However, some degree of catabolism was produced by these massive doses of the folliculoid in all groups.

The suppression of exudation, as well as the involution of the thymus, spleen, and lymph nodes are all most pronounced in the adrenalectomized-ovariectomized rats receiving estradiol and maintained with COLA alone, presumably because, in all these respects, estradiol and COLA mutually synergize each other, while DOCA tends to antagonize the corresponding effects of COLA. The comparative resistance of the intact animal is presumably to be ascribed to an endogenous secretion of DOCA-like mineralocorticoids by the animal's own adrenals.

In this series we again note some rather clear-cut dissociations in the estradiol effects. For instance, the thymus atrophy is virtually maximal in the intact estradiol-treated animals (group II), although their somatic growth rate is only slightly retarded and their lymph nodes did not undergo any significant atrophy (group II). On the other hand, the adrenalectomized-ovariectomized rats treated with COLA, which did not show a significantly greater thymus involution, lost an enormous amount of weight and underwent pronounced involution of the lymph nodes (group IV). Such a dissociation of the effects upon the different targets is also evident when we compare this latter group with the adrenalectomized-ovariectomized rats maintained on DOCA (group VI); in these, estradiol produces significantly less thymus involution, but greater catabolism and only slight lymph node involution.

These observations again confirm that the ovary, like the adrenal, imparts some resistance against the lethal effects of massive intoxication with a folliculoid hormone, however, at the same time the female gonad augments the thymolytic action of the estrogen. It is also evident that, in the absence of both steroid-producing endocrine glands, the actions of estradiol upon its various targets (body weight, inflammation, lymphatic organs) are not uniformly affected by corticoid therapy. We do not observe merely a general augmentation or diminution of the estradiol effects, but these can be dissociated, depending upon the type of corticoid given, in that certain actions are more markedly affected than others.

As we outlined in our introductory remarks, all the not ovariectomized rats receiving massive doses of estradiol developed large corpora lutea. Hence it was suspected that the imparting of resistance to the lethal effects, as well as the augmentation of the thymolytic effect of estradiol by the ovary, may be mediated through the secretion of progesterone. In order to obtain direct evidence in support of this theory, we now proceeded to examine the effect of progesterone injections upon the response to estradiol in adrenalectomized and ovariectomized rats.

Third experiment. After a series of preliminary experiments had shown that about 40 micrograms per day of estradiol are sufficient to induce 100 per cent mortality in adrenalectomized-ovariectomized rats (kept under our experimental conditions without

TABLE IV.—INTERACTIONS BETWEEN ESTRADIOL AND CORTICOIDS (FOURTH EXPERIMENT)

Group	Treatment			Final body weight, gm.	Weight gain, per cent	Exudate, ml.	Thymus, mgm.	Spleen, mgm.	Mortality, per cent
	Adrenal	Ovary	Hormone*						
I	Adr-X	Intact	Estradiol	148 ± 3.5	−6.8	4.5 ± 0.9	212 ± 18.7	615 ± 42.4	0
II	Adr-X	Ov-X	Estradiol	133 ± 1.6	−17.0	3.4 ± 0.5	208 ± 20.3	423 ± 29.7	60
III	Adr-X	Ov-X	Estradiol + progesterone	146 ± 2.8	−8.0	4.3 ± 0.8	132 ± 12.3	579 ± 21.7	0
IV	Adr-X†	Ov-X	Estradiol	159 ± 3.2	−0.9	7.3 ± 1.7	286 ± 12.5	549 ± 33.0	0

*In all groups the daily dose of the steroids listed in this column was the same, namely: estradiol 10 μgm. and progesterone 5,000 μgm.
†Since these animals received no corticoid therapy, they had to be given 1 per cent NaCl as a drinking fluid for life maintenance.

any substitution therapy), it was decided to use this lower dose in order to detect the presumably less pronounced life-maintaining effect of progesterone.

It will be noted that the mortality rate among the untreated adrenalectomized-ovariectomized rats was 30 per cent (group I), while none of the progesterone-treated animals succumbed (group III). The estradiol-treated rats all died before termination of the experiment (group II), while in the rats receiving progesterone in addition to estradiol the mortality was only 70 per cent. While progesterone thus offered at least partial protection against the lethal effects of estradiol, it aggravated the thymolytic effect of the latter. This aggravation cannot be deduced, in the present experimental series, from a comparison with corresponding rats treated with estradiol alone (group II), since these all died. It is evident, however, if we compare the very atrophic thymus of the group receiving treatment with both hormones (group IV) with that of the merely estradiol-treated adrenalectomized-ovariectomized rats, which were maintained with sodium chloride (group V). It may be argued, however, that sodium chloride itself merely counteracted the thymolytic action of estradiol more intensely than progesterone. Therefore, the experiment was repeated under comparable conditions with a smaller dose of estradiol, in an experiment of shorter duration, so as to obtain an adequate survival rate even in estradiol-treated adrenalectomized-ovariectomized rats receiving no form of substitution therapy.

Fourth experiment. In the fourth experimental series we administered 10 micrograms of estradiol per day. Progesterone was again given at the dose level of 5,000 micrograms in the form of a microcrystal suspension, but this time it was administered in 1 milliliter of water subcutaneously, in order to permit a better distribution and hence presumably a better absorption rate, despite the comparatively large amount. The experiment was terminated on the ninth day (rather than, in the usual manner, on the twelfth day) to make certain of an adequate survival rate.

It will be noted, first of all, that again the merely adrenalectomized rats survived treatment with estradiol much better (group I) than the adrenalectomized-ovariectomized animals (group II). Among the latter, 60 per cent had died and the remaining animals were all extremely ill when the experiment was terminated, while the adrenalectomized-ovariectomized rats, receiving the same amount of estradiol but simultaneously treated with progesterone (group III), were all alive and in good condition. Although, during the comparatively short period of 9 days, this small dose of estradiol did not produce complete thymus involution, nevertheless the mean weight of the gland was significantly lower in the animals treated with estradiol and progesterone than in any other group. It will also be observed that treatment with 1 per cent sodium chloride did not significantly protect the thymus against the atrophy produced by estradiol, although it prevented mortality (compare groups II and IV).

From experiments 3 and 4 it may be concluded that progesterone protects the adrenalectomized-ovariectomized rat against the lethal effects of estradiol intoxication but, at the same time, it augments the thymolytic effect of this folliculoid hormone. This is all

TABLE V.—INTERACTIONS BETWEEN CORTISOL AND PROGESTERONE (FIFTH EXPERIMENT)

Group	Treatment			Final body weight, gm.	Weight gain, per cent	Exudate ml.	Thymus, mgm.	Spleen, mgm.	Mortality, per cent
	Adrenal	Ovary	Hormone*						
I	Adr-X	Ov-X	COLA	134 ± 3.2	−16.1	5 ± 0.9	134 ± 20.5	624 ± 77.9	0
II	Adr-X	Ov-X	COLA+ progesterone (1,000 μgm.)	136 ± 4.8	−14.4	6 ± 1.4	100 ± 17.3	395 ± 44.2	0
III	Adr-X	Ov-X	COLA+ progesterone (2,000 μgm.)	149 ± 3.1	−6.2	10 ± 0.2	139 ± 11.8	532 ± 44.0	0
IV	Adr-X	Ov-X	COLA+ progesterone (5,000 μgm.)	154 ± 3.6	−3.1	14 ± 2.4	169 ± 20.3	618 ± 68.4	0
V	Adr-X	Ov-X	COLA+ progesterone (10,000 μgm.)	152 ± 2.5	−3.1	13 ± 1.6	146 ± 20.0	631 ± 55.0	0

*In all groups, the daily dose of COLA listed in this column was the same, namely: 400 μgm.

TABLE VI.—INTERACTIONS BETWEEN CORTISOL AND PROGESTERONE (SIXTH EXPERIMENT)

Group	Treatment			Final body weight, gm.	Weight gain, per cent	Exudate, ml.	Thymus, mgm.	Spleen, mgm.	Mortality, per cent
	Adrenal	Ovary	Hormone*						
I	Adr-X	Ov-X	COLA+ cholesterol (5,000 μgm.)	134 ± 3.2	−15.7	0.85 ± 1.0	150 ± 21.3	427 ± 33.6	0
II	Adr-X	Ov-X	COLA+ progesterone (1,000 μgm.)	138 ± 2.6	−13.3	3.4 ± 1.2	133 ± 13.9	383 ± 19.6	0
III	Adr-X	Ov-X	COLA+ progesterone (2,000 μgm.)	149 ± 3.7	−6.3	5.0 ± 1.4	164 ± 16.4	513 ± 30.8	0
IV	Adr-X	Ov-X	COLA+ progesterone (5,000 μgm.)	155 ± 2.7	−2.5	5.4 ± 1.6	121 ± 14.5	467 ± 37.8	0
V	Adr-X	Ov-X	COLA+ progesterone (10,000 μgm.)	157 ± 3.3	−1.0	8.3 ± 2.4	138 ± 23.1	557 ± 31.3	0

*In all groups, the daily dose of COLA listed in this column was the same, namely: 400 μgm.

the more noteworthy, since progesterone alone does not exhibit any obvious thymolytic effect under our experimental conditions (compare groups 1 and 3 in Table III).

The effect of progesterone upon the splenic weight does not parallel the thymolytic action. This is in agreement with many of our earlier observations concerning the often quite independent behavior of the thymus (a purely lymphatic organ) and the spleen (which in its red pulp possesses also essentially different histologic elements).

It is noteworthy, furthermore, that the synergism between estradiol and progesterone, which is so obvious as regards the thymus, did not manifest itself with respect to exudation. Here again we see a dissociation between the various usual actions of estradiol, as a result of concurrent treatment with another steroid.

Having thus established that progesterone augments the thymolytic effect of estradiol, the question arose whether it would also increase the corresponding effect of cortisol. At the same time, it appeared of interest to establish what other influences this luteoid substance might exert upon the various actions of a glucocorticoid.

Fifth and sixth experiments. In view of the importance of this problem, two experiments were performed each on 5 groups of 10 adrenalectomized-ovariectomized rats, under essentially similar conditions but at different times.

It will be noted that the results of these two experiments were essentially the same, except that (perhaps due to some uncontrollable factors, occasioned by the circumstance that the two experiments were not performed at the same time) exudation was

considerably more pronounced in all groups of experiment 6 than in those of experiment 5.

In both these experiments, the rats receiving only COLA as a substitution therapy (whether they were given no other treatment, as in series 5, or cholesterol, a hormonally inert steroid, as in series 6) exhibited the greatest loss of body weight and inhibition of exudation. Simultaneous treatment with increasing doses of progesterone counteracted this catabolism, as well as the antiphlogistic effect of cortisol, in proportion with the amount of the latter hormone given. On the other hand, the thymolytic action of cortisol was not significantly influenced by concurrent progesterone treatment, under our experimental conditions, in either of the two series.

It is evident that the effect of progesterone upon the same target-organ changes, caused on the one hand by estradiol, on the other by cortisol, differs significantly under our experimental conditions. Progesterone greatly increases the thymolytic effect of estradiol but not that of cortisol. On the other hand, progesterone actively inhibits the antiphlogistic action of cortisol but not of estradiol.

SUMMARY

Experiments on rats were performed to examine the rôle of the adrenals and ovaries in resistance to massive doses of estradiol. The mortality rate was used as an indicator of systemic resistance as such, exudation (granuloma pouch technique) to assess antiphlogistic actions, while the weights of the thymus and spleen acted as indicators of lympholytic actions.

The main results of these investigations were the following:

1. Merely adrenalectomized rats survive intoxication with estradiol much better than simultaneously adrenalectomized and ovariectomized animals; however, the thymus undergoes more pronounced atrophy in the former than in the latter.

2. In the absence of both the adrenals and the ovaries, neither cortisol acetate (COLA) nor desoxycorticosterone acetate (DOCA) offers as good a protection against estradiol intoxication as does combined treatment with both these corticoids.

3. By itself, progesterone does not exert any noteworthy thymolytic effect in adrenalectomized-ovariectomized animals, but it greatly enhances the thymus atrophy which can be induced in them by estradiol. At the same time, progesterone protects the adrenalectomized-ovariectomized rat against the lethal effect of estradiol intoxication. With respect to both the effects mentioned, progesterone simulates the effect of an intact ovary.

4. The thymolytic effect of COLA is not consistently influenced by simultaneous progesterone treatment in the adrenalectomized-ovariectomized rat; however, the catabolic and antiphlogistic actions of COLA are significantly inhibited by progesterone. From this it is evident that the effect of progesterone upon the same change (e.g., thymus involution, loss of body weight) differs significantly depending upon the manner in which the change was produced (e.g., estradiol or cortisol overdosage).

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BIOLOGIC FALSE POSITIVE REACTIONS FOR SYPHILIS IN PREGNANCY AS DETERMINED BY THE TREPONEMA PALLIDUM IMMOBILIZATION TEST

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PREGNANT WOMEN with reactive standard serologic tests for syphilis (STS) in the absence of clinical evidence of the disease, have always presented a difficult diagnostic problem. As a protection to both mother and infant, treatment is instituted pending diagnosis, and a stigma of syphilis is thereby placed upon the mother. With the development of the Treponema pallidum immobilization (TPI) test described by Nelson and Mayer, a valuable procedure has become available for differentiating the biologic false positive (BFP) reactions from those due to infection with Treponema pallidum. As a result of observing a high percentage of BFP reactions among sera from pregnant women with reactive STS, a study was carried out to determine if pregnancy could be a factor responsible for nonspecific reactions.

MATERIALS AND METHODS

TPI tests were performed on sera from pregnant and nonpregnant women according to the method described by Boak and Miller (1). In the majority of the pregnant women on whose sera the results of the TPI test were negative, a second sample was obtained approximately 3 months later and similarly tested in order to rule out the possibility of primary syphilis at the time of initial testing. Duplicate tests were carried out on each specimen in order to eliminate possible errors.

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RESULTS

TPI tests were completed on sera from 400 pregnant and 400 nonpregnant women with reactive STS. Two hundred and ninety-two or 73.0 per cent of the pregnant women and 244 or 61.0 per cent of the nonpregnant adult females were TPI negative (Table I). Thus, the ratio of negative TPI tests in the pregnant group exceeds that in the nonpregnant group by 12.0 per cent, a statistically significant difference. Standard serologic tests for syphilis were performed on the same sample of serum in 127 of the pregnant women with negative TPI tests. Seventy-nine or 62.6 per cent still showed reactivity in 1 or more of the tests, and 36 or 28.3 per cent had become nonreactive. Anticomplementary reactions were obtained in 12 specimens (Table II). When the standard serologic tests were performed on the same sample of serum from 54 of the pregnant women with positive TPI tests, 53 or 98.1 per cent still exhibited reactivity, and 1 or 1.9 per cent had become nonreactive. The prior serologic tests for syphilis on sera from 295 pregnant women with negative TPI tests are shown in Table III. The results of the TPI tests on the second sample of serum obtained from the pregnant women 3 months after the first specimen was collected differed in only 1 instance in which the initial test was doubtful, and the second was positive.

DISCUSSION

The importance of accurate diagnosis in the management of pregnant women with

TABLE I.—COMPARISON OF TPI TESTS ON 400 PREGNANT AND 400 NONPREGNANT WOMEN WITH REACTIVE SEROLOGIC TESTS FOR SYPHILIS

Results of test	*Pregnant*	*Nonpregnant*
Negative	292	244
Positive	103	154
Doubtful	5	2
Total	400	400
Per cent negative	73.0	61.0

TABLE II.—COMPARISON OF RESULTS OF STS ON SERA FROM 127 PREGNANT WOMEN WITH NEGATIVE TPI TESTS

Results of test	*Previous to TPI test*	*Identical serum sample*
Reactive	125	79*
Nonreactive	0	36
Anticomplementary	2	12
Per cent nonreactive	0	28.3

*One or more of the following tests was positive: VDRL, Kahn, Kolmer, cardiolipin Kolmer, cardiolipin Kline.

TABLE III.—RESULTS OF STS ON SERA FROM 295 PREGNANT WOMEN WITH NEGATIVE TPI TESTS*

	Results			
STS	*Reactive*	*Non-reactive*	*Anti-complementary*	*Per cent reactive*
Kolmer (lipoidal)	105	153	15	40.7
VDRL	80	90	—	47.1
Kolmer (cardiolipin)	50	31	15	52.1
Kline	12	5	—	70.6
Kahn	138	55	—	71.5
Mazzini	63	9	—	87.5

*The majority of STS were carried out in several laboratories and not on the same sample of serum.

reactive STS and no signs or symptoms of syphilis, coupled with the low specificity of such tests as shown in this study, enhance the value of the TPI test as a diagnostic aid to the physician. Although the reproducibility of results on the same serum sample has been questioned by Olansky and by Portnoy and their associates, it has been established at 97.4 per cent in this laboratory (2). The larger number of BFP reactors in the pregnant as compared to the nonpregnant women support the hypothesis that in some cases pregnancy, or an unknown factor associated with pregnancy, results in an alteration of the serum constituents so as to cause reactivity with the lipoidal antigens employed in the standard tests for syphilis. Although data are not yet available on the results of the STS on these patients following delivery, the reversion without treatment of reactive STS to nonreactive during the period of pregnancy in 28.3 per cent of the cases with negative TPI tests lends further support to the fact pregnancy in certain women causes a false positive serologic test for syphilis. A study to determine whether these changes occur in the protein or nonprotein fractions of these sera is under investigation in this laboratory.

SUMMARY

1. Seventy-three per cent of 400 pregnant women as compared to 61.0 per cent of 400 nonpregnant women with reactive STS were shown to have negative TPI tests. The difference of 12 per cent is statistically significant.

2. Seventy-nine of 127 sera from pregnant women with reactive STS exhibited reactivity in 1 or more of the STS performed on the sample of serum submitted for the TPI test, while 36 had become nonreactive, and 12 showed anticomplementary reactions.

3. The standard serologic tests for syphilis on serum from 295 pregnant women on whom the TPI was negative indicate a lower specificity for lipoidal than for cardiolipin antigens employed in flocculation tests.

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A REVIEW OF 306 CASES OF ENDOMETRIAL CARCINOMA

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THREE HUNDRED AND SIX CASES of endometrial carcinoma have been diagnosed at the Royal Victoria Montreal Maternity Hospital during the years 1926 to 1953 inclusive, and for purposes of comparison this interval has been divided into three parts, namely, 1926 to 1938 inclusive, 1939 to 1948 inclusive, and 1949 to 1953 inclusive. Approximately the same number of cases were seen during each period, and so some conclusions can be drawn from the results of our treatment and changes in our attitude toward the management of this disease can be detected.

The first observation to be made is relative to the number of cases in each period, for the first two periods are 13 years and 10 years respectively, and the last period is only 5 years, and yet the number of cases is approximately the same in each. This does not indicate, however, that this disease is becoming more common in Montreal, but is explained by the fact that in the last 10 years we are doing almost twice as much gynecology as before. This, at least, explains most of the increase, but some of it is also due to the increased life span, which is rapidly approaching 70 years of age for women. Of the entire 306 cases only 5 cannot be traced and are included in this series as fatalities.

Unlike carcinoma of the cervix, endometrial carcinoma appears to be primarily a disease of the better economic group, since well over 80 per cent of our series were admitted to the hospital under the care of a private gynecologist. It is, nevertheless, entirely likely that this finding is due to the fact that the peak age incidence is between 55 and 60 years, thereby occurring in patients who are more secure financially and better able to afford the services of a private physician. In our series (Table I) the peak age ranges for the periods 1926 to 1938, 1939 to 1948, and 1949 to 1953 were respectively 50 to 60, 46 to 60, and an even distribution between 46 to 80 years. A few cases occurred in patients under 40 years of age; the youngest patient was 26. However, in patients of from 45 years of age onward, there was a sudden and marked increase in the incidence which, coupled with the fact that a large number of these patients menstruate later than the average, as many investigators have pointed out—Randall says that 56.7 per cent of his series which he reported in 1951 menstruated after the age of 50—emphasizes the importance of not dismissing any irregular bleeding habit as due to menopausal behavior. Indeed, it is very discouraging to realize that it is the common belief among women that irregular bleeding in the forties means the change of life, allowing precious time to be lost before the institution of therapy. It is our practice never to pass off irregular vaginal bleeding, no matter how scant this may be, in a woman over 40 years of age, and under no circumstance will hormones be employed before a thorough diagnostic examination and curettage have been performed. As Parsons points out: "About 25% of all cancer arising in the body of the uterus will appear before the menopause."

Nearly all authors have drawn attention to the high incidence of diabetes, obesity, and relative infertility among patients with endometrial carcinoma. Table I shows the number of diabetics for the respective peri-

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Aided by a grant from the Cancer Research Society Inc.

TABLE I.—AGE PEAKS, MEDICAL COMPLICATIONS, GRAVIDITY, MENOPAUSE IN 306 CASES

	1926–1938 (95 cases)	*1939–1948 (114 cases)*	*1949–1953 (97 cases)*	*1926–1953 (306 cases)*	*Per cent of total*
Age peaks, years	50–60	46–60	Even 46–80		
Medical complications					
Cardiovascular disease	9	23	23	55	18.0
Diabetes	1	14	17	32	10.5
Nulligravida	35	28	26	89	29.1
Age of menopause					
Before 43	6	11	7	24	7.8
43–52	49	53	51	153	50.0
After 52	10	16	17	43	14.0
Unknown	30	34	22	86	28.1

ods, the single one occurring in the 1926 to 1938 interval being most unusual and probably reflecting the period when preoperative blood sugars were a rarity. McGarvey and Gibson have said that diabetes is 3 to 4 times more frequent among individuals with endometrial carcinoma than among the general population. Our figures seem astonishingly high. Cardiovascular disease, mainly hypertension, is also reported by these authors to be more common than expected for the same age groups (Table I).

With regards to infertility, McGarvey and Gibson state that while 4 out of 5 patients in their series were married, 51.6 per cent of them were unable to conceive. As long ago as 1900, Cullen noted this feature, and although our figures are not nearly as high, they are, nevertheless, approximately 3 times the figures for the general population. The obvious conclusion, therefore, is that there must be some endocrine imbalance which may be actually causative in the production of endometrial carcinoma or at least sets the stage for its development. It is no wonder, then, that most of the literature dealing with endometrial carcinoma since 1950 has been referable to the etiology of this disease.

The diagnosis of endometrial carcinoma involves first of all the proper education of the medical student, the practicing physician, and the female public, for this is the first line of attack against cancer, namely, early recognition. The second step is to utilize the various methods of diagnosis which are: (1) a careful history, (2) a thorough pelvic examination, (3) colpocytology, and (4) a thorough curettage—a fractional curettage being the method of choice. As mentioned before, a relatively large number of women who develop carcinoma of the endometrium are still menstruating and, as Kelly points out, 90 per cent of endometrial cancer patients studied by him presented some sort of abnormal vaginal bleeding. In our series, the outstanding symptom was bleeding which varied all the way from slight "spotting" to frank hemorrhage. In a moderate number of cases, leucorrhea with or without any appreciable odor was the only complaint, and, in a smaller number still, lower abdominal pain was the presenting symptom, although this usually indicated advanced disease. In only a small number of patients (22 out of 306) was there any significant weight loss. Table I shows the number of patients who ceased menstruating before 43, between 43 and 52, and after 52 years of age. It is interesting to note that in 43 known cases of the 306 the patients were still menstruating after the age of 52 years.

All of the endometrial carcinomas were adenocarcinomas, only a few showing acanthomatous changes. The uterus was enlarged in almost every case, except the very early ones which were found accidentally because of hysterectomy for descensus or some other pelvic pathologic condition. The number of polypi encountered did not seem unusually high although particular attention was not paid to this aspect.

In recent years cytologic examination of the vaginal pool contents or of cervical scrapings has come to the fore. At our hospital this examination as a screening test for

the early detection of cervical carcinoma is very reliable, but with endometrial carcinoma our accuracy is in the neighborhood of 65 to 70 per cent, a figure which can be improved, as some British clinics claim. If, however, this test is positive, it has a definite significance, whereas a negative report is of no particular value and the other diagnostic aids of history and curettage should be resorted to.

The staging of endometrial carcinoma is much more unsatisfactory than that of cervical carcinoma, and a number of classifications have been recommended; Kottmeier has recently discussed this subject. For our review we chose the International Classification of Endometrial Carcinoma which is:

Stage 0. The cancer is localized and still within the endometrium itself and not spread beyond into the uterine wall, e.g., a polyp showing malignant changes or a circumscribed adenoma malignum; in other words, the counterpart of carcinoma in situ of the cervix. There were 34 such cases in this group of 306, a percentage of 11.1.

Stage 1. The growth is confined to the uterus and may have invaded the myometrium; as a rule the uterus is enlarged but regular in outline unless fibroids are present. These cases are further divided into:

Group A—operable cases.

Group B—operation inadvisable because of some associated complication such as diabetes, cardiovascular disease, or obesity. There were 182 cases in group A and 41 cases in group B.

Stage 2. The growth has spread beyond the boundaries of the uterus, e.g., the broad ligaments, the cervix, vagina; 47 of the patients were in this stage.

It is at once apparent that this classification does not answer all purposes and leaves much to be desired, especially in the stage 1 cases, for what one surgeon may consider inoperable, another may operate upon without hesitation. Moreover, with the great improvement in the management of diabetes, anesthesia, and modern surgical care, many more cases than before are now operable; and so the tendency toward more and more surgery is inevitable. Thus it is that 116 of 146 stage 1 cases in the years 1926 to 1948 were categorized as stage 1A as seen in Table II; and the 5 year survival rate was 66.4 per cent. It is also gratifying to note that there were 37.8 per cent 5 year survivals among the stage 2 group. Of the stage 1B patients, only 40 per cent survived 5 years. This indicates that a high proportion of deaths were due to causes other than cancer; in fact, 35 of the 306 patients, or 11.4 per cent, died from other causes without clinical evidence of recurrence.

TABLE II.—RELATION OF STAGE OF ENDOMETRIAL CARCINOMA TO SURVIVALS FOR YEARS 1926–1948

Stage	*No. of cases*	*Per cent of cases*	*No. of 5 yr. survivals*	*Per cent of 5 yr. survivals*
0	26	12.4	21	80.8
1A	116	55.5	77	66.4
1B	30	14.4	12	40.0
2	37	17.7	14	37.8
Total	209	100.0	124	59.3

TREATMENT AND ITS RESULTS

The treatment of endometrial carcinoma at our hospital has been guided in large part by the physical health of the patient, the stage of the disease when first diagnosed, and to some extent by the technical skill of the gynecologist. In the more recent years, however, it has become increasingly clear that surgical extirpation of the uterus, if nothing else, is a most important part of the therapy. Since 1949 (Table III) 50 cases have been treated by surgery alone, and of a total of 95 cases, in 66 total hysterectomy and bilateral salpingo-oophorectomy have been performed, that is, only 16 patients have had surgery and radiation therapy combined. Table III reveals the relation of treatment to the percentage of 5 year survivals in the periods 1926 to 1938, 1939 to 1948, and 1926 to 1948; we believe these data add strength to the advisability of making surgery a part of the therapy.

TABLE III.—RELATION OF TREATMENT TO PERCENTAGE OF 5 YEAR SURVIVALS

Years	*Radiation only*	*Surgery only*	*Radiation plus surgery*	*Surgery plus x-ray*
1926–1938 inclusive	60.4	66.6	74.3	50.0
1939–1948 inclusive	44.2	68.7	73.7	80.0
1926–1948 inclusive	48.0	67.8	73.0	66.6

TABLE IV.—RELATIONSHIP OF THERAPY TO SURVIVALS—ALL STAGES

		Survival			
		−5 years		+5 years	
Treatment	*No.*	*No.*	*Per cent*	*No.*	*Per cent*
1926–1938, 95 CASES					
Surgery.....	54	16	29.6	38	70.4
Radiation.....	41	18	43.9	23	56.1
1939–1948, 114 CASES					
Surgery.....	59	19	32.2	40	67.8
Radiation.....	55	32	58.2	23	41.8

Our radiotherapeutic technique has varied slightly over the years. In the earlier years, when we were learning how to use radium, it was not uncommon to find radium in doses of 1,800 to 2,500 milligram hours and usually without deep x-ray supplement. These admittedly were the apparently early cases with a small localized lesion. As time has passed, however, and the control of gynecologic cancer has come more and more under the wing of one gynecologist, it has become evident that when one is dealing with corpus cancer, or any other cancer for that matter, it is useless sending a boy to do a man's job. Our present practice, therefore, is to use a minimal radium dose of 4,500 milligram hours, if the uterus is small, and up to 7,000 milligram hours if it is large. A part of this radiation, however, is directed at the cervix and vaginal vault by having a plaque placed against the portio of the cervix. If surgery is to follow the radium therapy, then 6 weeks are allowed to elapse. If deep x-ray is employed it is instituted while the patient is still in the hospital for the radium. We have not as yet been administering vaginal radium to patients who have been treated primarily by total hysterectomy as radiotherapists have been advocating and doing in an effort to reduce recurrences in the most common site, the vaginal vault.

The relationship of therapy to survivals is demonstrated in Table IV and illustrates clearly the important role of surgery. The cases grouped under "surgery" consist of those patients who have had hysterectomy and usually bilateral salpingo-oophorectomy either alone or in conjunction with radium or deep x-ray. Those grouped under "radiation" have received only radium, or radium plus deep x-ray, or x-ray only.

Table V gives the relationship of treatment to the percentage of 5 year survivals in the various stages. Most of the stage 0 cases were treated surgically only, and even here the figure is better than when radiation alone is used. Stages 1A and 2 cases were represented by adequate and similar numbers of patients, and the outstanding feature is the superiority of the surgical approach to the problem even when spread of tumor is known to have gone beyond the limits of the uterus itself.

The complications encountered in all forms of treatment were relatively few. Peritonitis (5 cases) occurred following surgery with the exception of 2 cases, one of which was due to a perforation at the time of radium insertion, the other apparently a flare-up of a pelvic inflammation following irradiation. The urologic complications (10 cases) were due to tumor involvement either of the bladder, the ureters, or both of these structures, and were usually encountered in the advanced cases.

The operative mortality for the entire period (1926 to 1953) is 4.5 per cent, but in the last 5 years (95 cases) there has been no operative loss.

DISCUSSION

When one discusses the problem of treatment of endometrial carcinoma, there is always the question of radiation versus surgery; and, while most gynecologists will argue in favor of surgery, there are some who claim and statistically substantiate that radium and x-ray therapy can by themselves produce just as good results as surgery whether used alone or in conjunction with radium. The chief exponents of radiation therapy are to be found at the Radiumhemmet in Stockholm, Sweden, but other radiotherapists are thinking similarly, and many of them state that adenocarcinoma of the endometrium is just as radiosensitive as is squamous carcinoma of the cervix. Kottmeier says, for example, that "primary radiotherapy adequately adminis-

tered is just as justifiable as is primary surgery in the treatment of corpus cancer." But the words "adequately administered" in his opinion and in his practice involves an elaborate, tedious, and technically tricky procedure of "packing" the uterine cavity with numerous small capsules containing the radium. By so doing, he can fill the uterus no matter how irregular the cavity may be and so create an even distribution of radiation to the cancerous organ. This is an ideal radiotherapeutic approach to the problem, and other gadgets have been employed by other cancer centers; thus the Marie Curie Hospital in London uses a central tube with two cornual applicators, while Strickland, of the Mount Vernon Hospital, uses a flexible metal tube with cobalt rods in an effort to give even radiation to the uterus. Our technique utilizes the Swanberg tube and plaque, that is, a single tube in the uterine cavity and a plaque against the cervix. When one compares the results of therapy, however, one finds that the figures, except those from a few clinics notably in Sweden, are better when surgery is employed, and the surgical approach does not seem to matter. Van Bouwdijk Bastiaanse, for example, reported in 1952 a series of 264 cases of carcinoma of the body of the uterus in which only 33 had abdominal hysterectomy plus bilateral salpingo-oophorectomy because of the large size of the uterus. In the remaining 231 cases he performed vaginal hysterectomy plus bilateral salpingo-oophorectomy and claimed an absolute 5 year cure rate of 66.9 per cent. As McKelvey of Minneapolis remarks in his review of this paper: "Here is interesting evidence that whatever the surgical approach, high surgical procedural rates are possible and safe, producing a high cure rate." No one can deny that radiation therapy can produce satisfactory results if an adequate and even dose of radiation is administered, but most reports, including this one, indicate that surgical extirpation of the uterus, tubes, and ovaries forms an important part of the therapy. The absolute 5 year cure rate in this present series for the

TABLE V.—RELATIONSHIP OF STAGE AND THERAPY TO PERCENTAGE OF 5 YEAR SURVIVALS

Stage	Treatment: Surgery Per cent	Treatment: Radiation Per cent
1926–1938, 5 YEAR SURVIVALS		
0	75.0	100.0
1A	75.0	66.6
1B	100.0	42.8
2	44.4	33.3
All	70.4	56.1
1939–1948, 5 YEAR SURVIVALS		
0	90.9	66.6
1A	62.2	57.9
1B	100.0	30.0
2	55.5	20.0
All	67.8	41.8
1926–1948, 5 YEAR SURVIVALS		
0	84.2	71.4
1A	68.5	62.8
1B	100.0	33.3
2	50.0	26.3
All	69.0	47.9

periods 1926 to 1948 inclusive is 59.3 per cent. This figure includes 6 patients who received no treatment because of the terminal stage of the disease when first seen, and 3 patients who were lost and have been counted as fatalities. If these 9 patients are not included in the evaluation of our results, we find that the 5 year survival rate for all forms of treatment is 62.0 per cent. Surgery was part or all of the treatment given 113 patients, 69.0 per cent of whom survived for 5 years or longer. Eighty-seven patients were treated by radiation only, and the 5 year survival rate is 52.9 per cent. With improved surgical technique and preoperative and postoperative care it is hoped that the overall 5 year survival rate will be raised much higher in the future. It is entirely possible that some form of radical hysterectomy with lymphadenectomy may be needed. We are very ready to agree that it is really unfair to compare the results of surgical and radiation therapies, for the latter is usually employed in those cases in which the surgical approach is either inadvisable or technically impossible. Nevertheless, we do feel that the reports of others plus our own records justify the conclusion that surgical removal of the uterus, tubes, and ovaries should be the first and probably the only consideration in the treatment of endometrial carcinoma.

CONCLUSION

From the excellent follow-up of 306 cases of endometrial carcinoma which were diagnosed at the Royal Victoria Montreal Maternity Hospital, it would seem that surgical extirpation of the pelvic genital organs offers the best chance of effecting a permanent cure. In this series, radium plus surgery has given better 5 year results, but surgery alone has offered a much greater chance of an apparent permanent cure; radiation alone leads to the worst results. We, therefore, advocate that surgical removal of the genital organs should be carried out whenever it is possible.

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A CLINICOPATHOLOGIC STUDY OF POSTERIOR PENETRATING GASTRIC ULCERS

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SOME ULCERATING LESIONS of the stomach are so evidently ulcerating carcinomas that the diagnosis can be made with a high degree of certainty on gross inspection alone. Others are "punched out" in appearance, do not present the heaped-up edges characteristic of malignant ulcers, and might be described as "ulcers of the peptic type" for want of a better term. It has been the experience of Mayo, Shoulders and Lischer, Marshak and associates, Musgrove, and others that ulcerating lesions of the posterior wall of the stomach may become very large and may present attachment to nearby structures, developments that suggest malignant lesions although they are really benign. The present paper describes the results of a clinicopathologic study of a group of penetrating ulcers of the peptic type which were limited to the posterior wall of the stomach and which were resected surgically.

MATERIALS AND METHODS

Records from the surgical files of the Mayo Clinic for the 6 year period, 1944 to 1949 inclusive, of patients having gastric ulcers which satisfied the following criteria were selected: (1) Each ulcer was wholly confined to the posterior wall of the stomach. (2) Each ulcer was penetrating to the extent that sharp dissection was required to detach its base from adherent structures. (3) Each ulcer was of the peptic type, which is to say that, on inspection of the opened stomach, the appearance of the ulcer in no way resembled a grossly recognizable carcinoma undergoing ulceration.

Ninety-one cases fulfilled the suggested criteria. Data collected from the records and from gross and microscopic study of the surgical specimens form the basis for this report.

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Abridgment of thesis submitted by Dr. Caruolo to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

RESULTS

During the 6 years covered by this study, 1,066 patients with carcinoma of the stomach were treated at the clinic by removal of all or part of the stomach and 828 patients with benign gastric ulcers were treated surgically. Of the 91 gastric ulcers which fulfilled the criteria previously defined, 3 (3.3 per cent) were malignant. The 3 malignant ulcers represent 0.3 per cent of the 1,066 resectable carcinomas of the stomach; the 88 benign posterior perforating ulcers represent 10.6 per cent of the 828 benign gastric ulcers.

Sixty-seven (73.6 per cent) of the 91 patients were men; 24 (26.4 per cent) were women. The oldest patient, a man, was 76 years of age; the youngest, a woman, was 25 years of age. The average duration of symptoms was 8.3 years though 1 patient denied knowledge of illness until 5 days before admission and 5 patients claimed that symptoms had been present since childhood. Only 1 patient gave a history suggestive of previous acute free perforation of a gastric ulcer. Seventeen patients had previously undergone abdominal operations such as exploration, cholecystectomy, local excision of a gastric ulcer, and the like because of symptoms similar to those present when they were first seen at the clinic. The commonest

TABLE I.—TYPES OF PROCEDURES PERFORMED

Basic	*Cases*	*Per cent*	*Additional procedures*	*Cases*
Billroth II type with posterior anastomosis...	31	34.1	Partial pancreatectomy	1
			Splenectomy	1
			Enteroenterostomy	1
Billroth II type with anterior anastomosis...	29	31.8	Enteroenterostomy	1
Billroth I type...	21	23.1	Partial pancreatectomy	1
			Transverse colectomy	1
Excision of ulcer.	7	7.7	Gastroenterostomy	3
			Gastroenterostomy and vagotomy	1
			Excision of leiomyosarcoma	1
Total gastrectomy..	3	3.3		
Total.....	91	100.0	Total	11

complaints were of epigastric pain (72.6 per cent), hematemesis or melena or both (39.6 per cent), vomiting (38.5 per cent), and pain referred to the back (34.1 per cent). Of the 36 patients who had experienced hematemesis or melena or both, 8 presented evidence of duodenal ulcer in addition to gastric ulcer; in these patients the source of bleeding was doubtful. The remaining 28 patients presumably bled from their gastric ulcers.

Many of these patients were described as being cachectic. The average loss of weight was 14.9 pounds (6.45 kgm.) and half of the patients had lost 20 pounds (9.1 kgm.) or more. Anemia was a frequent finding. Gastric analysis performed with use of the Ewald test meal showed an average total acidity of 48.5 clinical units and an average free acidity of 34.5 clinical units. In 5 patients free acid was not produced in response to this type of stimulation; these patients proved to have benign ulcers. Significant gastric retention was unusual, only 9 patients having more than 200 milliliters of contents in the stomach after an overnight fast. Roentgenograms and fluoroscopic studies of the stomach and the duodenum after ingestion of barium were made in all instances. In all but 4 cases the ulcers were detected roentgenologically. In 26 patients (28.6 per cent) the roentgenologist considered the lesions to be definitely or probably malignant; in 48 patients his diagnosis of gastric ulcer was unqualified, and in 13 patients the lesions were considered benign. The final preoperative clinical impressions likewise often stressed the possibility of carcinoma of the stomach, this diagnosis being made in 36 cases (39.6 per cent). In all 36, the lesions were found to be benign.

In 9 of 38 instances in which the surgeon recorded his impression of the pathologic condition, based on gross inspection before the ulcers were removed, the lesions were considered malignant; subsequent microscopic examination, however, proved them to be benign. The types of operations performed in the 91 cases are shown in Table I. One patient died after total gastrectomy when volvulus of the small intestine with infarction of the intestine developed resulting in peritonitis. This death made the hospital mortality rate about 1 per cent. In several instances thickening and inflammation of the transverse mesocolon made anastomosis between stomach and jejunum anterior to the colon obligatory. Three total gastrectomies were performed because the position and huge size of the ulcers, together with the associated deformity of the stomach, prevented performance of local excision of the ulcers or of subtotal gastrectomy.

TABLE II.—COMPARISON BETWEEN THE SIZES OF BENIGN POSTERIOR PENETRATING GASTRIC ULCERS AND BENIGN UNSELECTED GASTRIC ULCERS

Diameter of ulcers, cm.	*This series, per cent*	*Series of unselected gastric ulcers* (1), *per cent*
Up to 1.8.....	28.4	78.8
1.9 to 2.5.....	43.2	15.0
2.6 to 3.0.....	7.9	4.4
3.1 to 3.5.....	3.4	1.5
3.6 to 4.0.....	9.2	0.3
4.1 and over.....	7.9	0.0

PATHOLOGIC FEATURES

The ulcers, measured by the pathologists at the time of operation when the tissue was fresh, were often large: 72 per cent were greater than 1.9 centimeters in diameter, 28 per cent were greater than 2.5 centimeters, and 8 per cent were more than 4 centimeters. The tendency for ulcers of the pos-

terior wall of the stomach to become larger than ulcers elsewhere in the organ is well shown by a comparison of the sizes of ulcers in the present series of patients with those of ulcers taken without regard to their location in the stomach and reported by Alvarez and MacCarty (Table II).

Large amounts of fibrous tissue were found in the bases of the ulcers. In cases in which the ulcer was removed intact this tissue formed a discoid mass. In cases in which the base of the ulcer had to be left in place, the fibrous and granulation tissue took the form of a ring beneath the edge of the ulcer in the resected specimen. In many instances there was so much inflammatory tissue beneath the ulcer that the lesion gave the appearance of a tumor. In 1 case this "pseudotumor," as Ledoux-Lebard called it, measured 12 by 12 by 15 centimeters.

The ulcers most frequently became attached to the pancreas (Table III). Microscopic sections of the bases of the ulcers were examined in a search for pancreatic tissue; this was found in only 2 instances. Furthermore, except for the place of attachment of the gastric ulcer, the pancreas was described as normal in all cases. There was no clinical evidence of pancreatitis after operation in any case. Thus it appears, paradoxically enough, that neither the penetration of the pancreas by gastric ulcers nor the surgical dissection separating the ulcers from this gland is likely to be followed by clinically significant pancreatitis.

TABLE III.—SITES OF ATTACHMENT OF THE BASES OF THE ULCERS

Site of attachment of ulcer	*Cases*	*Per cent*
Pancreas alone	72	79.1
Pancreas and transverse mesocolon	9	9.9
Pancreas and liver	2	2.2
Pancreas and spleen	2	2.2
Pancreas and gastrosplenic ligament	1	1.1
Transverse mesocolon	3	3.3
Transverse colon	2	2.2
Total	91	100.0

COMMENT

It must be emphasized that the 91 gastric ulcers which form the basis for this study were carefully selected to exclude frank ulcerating carcinomas, and that the data must not be taken to indicate that the incidence of malignancy in all ulcerating lesions of the posterior wall of the stomach is only 3.3 per cent. But, when similar criteria are applied to the evaluation of even smaller ulcerative lesions that are located elsewhere in the stomach, as MacCarty has shown, microscopic examination discloses unsuspected malignancy in an incidence which approximates 10 per cent. The purpose of this presentation is to re-emphasize the fact that penetrating gastric ulcers, especially on the posterior wall of the stomach, can become very large, and can be associated with so much inflammatory reaction at the attachments to the pancreas, or sometimes other adjacent organs, that the resulting pseudotumor may mimic the gross appearance of a carcinoma. Furthermore, in our experience, it is impossible to be certain preoperatively, or on gross inspection at the time of operation, which of these lesions is truly malignant. Clinical diagnoses in this situation show the tendency to err in considering benign lesions as malignant lesions. Yet a clinical diagnosis of malignant disease was not made in any of the 3 patients in this series who proved to have malignant lesions. Though these 3 cancerous ulcers were large, measuring 3 by 3, 3 by 2.5, and 5 by 5 centimeters, respectively, the patients had not lost weight, had free acid present in the gastric contents, and had not presented roentgenologic evidence or gross findings which would distinguish them from the members of the group having benign lesions.

Two lessons to be learned from this group of patients are: (1) that a large fixed ulcerating lesion of the posterior wall of the stomach without obvious signs of malignant development, such as metastatic growth, which can be identified by biopsy and microscopic examination with the use of the frozen-section technique, will often be benign despite its size and appearance and (2) that probably the small group of malignant ulcers cannot be distinguished from the larger group of

benign ulcers by means of gross criteria alone. The best treatment is excision of the lesion by subtotal gastrectomy when possible, and the surgeon must be prepared to carry out this procedure despite the local fixation which may suggest an inoperable malignant lesion. In this way only can he avoid the errors of considering benign lesions as inoperable malignant lesions and of failing to remove a few malignant lesions whose fixation is caused by inflammatory tissue.

SUMMARY AND CONCLUSIONS

The following facts emerged from a study of 91 ulcerating lesions of the posterior wall of the stomach which, on gross inspection, were found to be of the "peptic" type and which had penetrated to become attached to adjacent structures:

1. The organ which these ulcers most frequently penetrated was the pancreas. Neither the ulcers themselves nor dissection of the ulcers from the pancreas, sometimes leaving the crater in situ, resulted in clinically significant pancreatitis.

2. Epigastric pain, hematemesis or melena or both, vomiting, and pain referred to the back were the commonest complaints of the patients in this series.

3. The history, physical findings, laboratory data, and results of palpation and inspection of these lesions at the time of operation often strongly suggested a diagnosis of carcinoma of the stomach.

The incidence of malignant disease, however, was only 3.3 per cent. It proved impossible to distinguish the few malignant lesions from the many benign ones at operation on the basis of gross criteria alone. It follows that the surgeon faced with a large, fixed ulcerating lesion on the posterior wall of the stomach without obvious signs of malignancy should remember that most lesions of this type are benign and should proceed with resection whenever possible to avoid the error of regarding the lesions as malignant and inoperable.

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EDITORIALS

OPERATIVE CHOLANGIOGRAPHY

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OPERATIVE CHOLANGIOGRAPHY entails an expenditure for equipment that is appreciable, and on the average requires personnel and the operating room for an additional 10 to 30 minutes per cholecystectomy. Should all hospitals supply this facility? What are the proved advantages and limitations to be considered by the surgical staff before urging this procedure on hospital management?

In the first place, the merit of the procedure will be measured not alone by the quality of equipment but more particularly by the co-operative planning between the radiologist and the surgical staff. Without this it cannot succeed. In addition, the method must be used with sufficient regularity to permit dependable interpretations and to eliminate technical error. The installation of adequate equipment does pose a problem to the average hospital's budget —although this hurdle should not be insurmountable.

The simplest operative cholangiography requires a mobile Potter-Buckey grid beneath the patient and a radiographic unit capable of operating within a range of 20 to 30 milliamperes and 60 to 80 kilovolts. The approximate cost of this minimum setup is about 2,500 dollars. The shortcomings of such equipment of low power are mainly those of penetration and speed. In the more elaborate facility there is incorporated into the surgical amphitheater a roentgen unit having a top kilovolt rating of 100 kilovolts or over and a milliampere output of from 300 to 500. These may be equipped with rotating anode tubes with small focal spots and frequently are integrated automatically with the movable grid on the operating table. Cassettes with par-speed screens give optimum detail and are preferred to screens of high speed. Such equipment would provide all of the latitude ordinarily available in the average x-ray department of most hospitals—but not ordinarily found in the operating room. Its cost is approximately 10,000 dollars installed.

Cholangiography performed by the first method, when done meticulously and by experienced personnel under the direction of the radiologist who is sufficiently interested in the problem and readily available, is usually satisfactory for rough surveys. It would demonstrate localized dilatation or obstruction of the common duct, congenital anomalies of the biliary tree, and the presence of large stones. With less dependence, it might reveal the presence of small stones. We are informed that there is under recent manufacture a mobile unit with an output rating of 300 milliamperes at 90 kilovolts, equipped with rotating anode tube. From the standpoint of both cost (approximately 5,000 dollars) and space, such a unit may serve to outmode those presently available.

There are advantages and certain limitations in the use of operative cholangiography. It can be reliably depended upon

(1) to demonstrate patency between the biliary tract and the duodenum, and (2) to determine the relative size of the extrahepatic and intrahepatic ducts. It affords valuable information in infants undergoing surgery for biliary duct atresia. The gallbladder is easily injected with contrast material and the ducts outlined. Operative cholangiography is also of great value in those instances in which one resorts to surgical exploration for prolonged jaundice suspected to be due to hepatitis but when obstructing stone or cancer cannot be ruled out. Here the intrahepatic obstruction results in an empty gallbladder and collapsed extrahepatic ducts, which can be quickly outlined with an operative cholangiogram by injecting contrast material into the gallbladder. This ductal pattern, combined with liver biopsy, will give a prompt and more complete answer than surgical exploration without prolonging the anesthesia or injuring the small empty duct, which in hepatitis is usually found to be embedded in edematous lymphadenopathy and is difficult to explore. Another practical usage is to determine a common ampullary channel with the pancreatic duct, as well as the presence of stricture or dilatation of the pancreatic duct in cases of chronic pancreatitis. The more inexpensive roentgen unit is adequate for these enumerated purposes.

A more frequent need is for a reliable method of determining the presence or absence of common duct stones at the time of cholecystectomy. Then there would be no need to open the common duct, with the chance of injury or resulting sequelae, except to remove the demonstrated offending stone. However, for this purpose its dependability will vary with the interest and ability of the professional team, the available equipment, and the frequency with which it is practiced. False positives and false negatives may be more confusing than helpful and may unnecessarily prolong the operation. Until a technique which provides reliable interpretation has been accomplished, the surgeon should put first reliance on his clinical judgment and open the duct in stone-suspect cases. Before we used operative cholangiography, we reported an analysis of 478 cholecystectomies for stone, in which we found we had openly explored the common duct in 40 per cent in order to discover stones in 20 per cent. In other words, we opened two ducts for each one we found to contain stones. The incidence of exploration has been since reduced in part by the help of lessons learned from this study[1] and in part by the institution since that time of operative cholangiography. Appropriate to the use of operative cholangiography is the fact that we found that the 76 common ducts which harbored stones (as well as 12 cases of fibrosis of the sphincter of Oddi) were in all but 4 instances dilated beyond the normal 8 millimeter diameter. We believe dilatation should be a chief indication for either open exploration or operative cholangiography.

This prompts the question of whether, in properly equipped centers, operative cholangiography should be employed as a routine in all patients at the time of cholecystectomy. In weighing such policy, we should remember that the test can be followed by untoward sequelae, such as reflux pancreatitis and chemical cholangitis. Furthermore, it involves an extra charge to the patient, and an additional operative time and manipulation. It would seem unnecessary when there is no clinical suggestion of common duct disease, and particularly in the presence of a normal-sized common duct. As stated, we believe that a stone cannot long reside in a duct without creating dilatation, and that the normal-sized duct should rarely require exploration —or cholangiography. Associated cholangitis, obstructive jaundice, or pancreatitis would be obvious exceptions to this rule but a nondilated duct in such instances is rare. Adequate exposure of the common duct is of course assumed; otherwise its size

[1]Baker, Joel W., and Koutsky, Joseph. The problem of common duct exploration at the time of cholecystectomy. West. J. Surg., 1951, 59: 495-503.

cannot be reliably established. Occasionally operative cholangiography may be of value in demonstrating that the duct is dilated and therefore under suspicion. We have substituted cholangiography for open exploration in those cases in which the demonstrated dilatation of the common duct is suspected of being a compensatory dilatation rather than due to stone. Such physiologic dilatation may result after cystic duct obstruction erases the gallbladder's function, just as it occurs after surgical cholecystectomy. This compensatory dilatation was the greatest source for our negative explorations. It should be noted that fibrosis of the sphincter of Oddi cannot be reliably ruled out by cholangiography.

The lack of operative cholangiography is realized most acutely by the surgeon when postoperative cholangiographic study demonstrates residual or overlooked stone. This unfortunate and embarrassing situation occurs in a reported incidence varying from 2 to as high as 24 per cent of ducts from which stones were removed at operation. It does seem to us, therefore, that when the facility is available, it should be routine in all cases in which open choledochostomy has been done to inject contrast media into the T tube and to take roentgenograms of the common duct for residual stone before closing the abdomen. However, even with the best x-ray available in the operating room, stones may still be missed. Waugh has mentioned that small stones, which become embedded in crypts near the ampulla of Vater and are missed when they allow probes and scoops and irrigating solutions to pass freely, may likewise allow nonviscous radiopaque solutions to pass without demonstrating a discrete filling defect. Another source of overlooked stones are those hiding or escaping at exploration into the intrahepatic ducts. Operative cholangiography may, with ideal techniques and multiple views, discover some of these stones. Norman found that too often these hepatic stones are not visible as negative shadows, but must be suspected from indirect signs, such as absence of filling of one hepatic duct when others are filled. This implies a correlating study of the normal pattern of these ducts. Even in these, Norman found a high percentage to be technically impossible of removal, and we have had a similar experience in several cases.

From now on those stones we miss at operation, either from lack of open exploration or operative cholangiography, may now be more readily proved in the postoperative period by the use of intravenous cholografin cholangiography, without waiting as in the past for jaundice or other obstructive symptoms. Such demonstration of these overlooked stones in the early postoperative period will be more incriminating than in the past when we did not have this method available.

Certainly it would seem a desirable goal that all hospitals make available in the operating room the same dependable techniques there that are used in the x-ray department for postoperative cholangiography, so that at least residual stones which can and will be demonstrated in the postoperative period can be demonstrated and recovered at the primary operation and not entail reoperation. This is an ideal which is becoming nearer the reach of the majority of hospitals. Although operative cholangiography is not a substitute for surgical judgment as to when the common bile duct should be opened, it proves most helpful in many cases.

CARCINOMA OF THE HEAD AND NECK: PLEA FOR MORE RADICAL SURGICAL EXCISION AND THE IMMEDIATE EMPLOY OF THE STEPS OF RECONSTRUCTIVE SURGERY

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ACTIVATED INTEREST by the American public in the fact that cancer is one of the leading causes of death has been reflected in the intensified research which is directed at solution of the etiology of carcinoma. It is within the realm of reasonable probability that these laboratory efforts may bring out a chemotherapeutic or immunity producing agent which will at least limit the rate of growth of cancer and its metastases. Meanwhile, carcinoma is looked upon as a parasitic disease which in the majority of cases falls within the scope of excisional surgery. Significant increase in recent years in the duration of postoperative survival without evidence of disease has offered some satisfaction in the intensified attack by surgeons on cancer. Resection of primary lesions together with regional nodes, i.e., those in the direct lymphatic routes of extension, has been the basic principle of this surgery, extended in selected cases to en bloc excision of lesion, nodes, and intervening tissue and even to the resection of metastases. The development of thoracic surgical techniques has advanced the surgery of breast cancer so that the final pathway of extension, formerly inaccessible, the mediastinal nodes, now may be excised with the mass according to the technique of Urban. There is a distinct feeling that the field of carcinoma of the head and neck, the oral cavity, and pharynx has not been subjected to the same degree of intensified clinical attack as have carcinomas in other portions of the human body. In all probability the fact that carcinomas of this region are caught in the interplay between specialists of widely different categories has been a factor in this. Nationwide uniformity in therapeutic method for malignant lesions of the oral cavity and head and neck is lacking. There still is strong controversy (for many of the intraoral carcinomas, as well as the skin carcinomas) as to whether a given tumor should be treated by x-ray, by radium, or by surgery. Lack of uniformity in the policies of leading hospitals and medical centers has not helped to clear up this situation. Unquestionably, the greatest deterrent to radical surgery as the ideal method of treatment has been the fear of or concern over the mutilating effect of such procedures. The competent surgeon hesitates to create gross facial defects even when the objective is the eradication of cancer, and the referring physician hesitates to recommend such treatment. As a result, less drastic and less effective modes of treatment are employed. Surgeons generally seem to be remiss in failing to master the reconstructive techniques of correction of defects of the head and neck. If the principles of reconstructive surgery are taken into consideration before radical surgery is employed, the surgeon will exercise much wider excision of carcinoma of the head and neck, thus creating background for the reporting of greatly improved follow-up results. This type of thinking is no different from that associated with the development of successful surgical extirpation of carcinomas of the interior cavities of the body. For instance, carcinoma of the pancreas was looked upon as an inoperable lesion until the ingenious reconstructive steps of the Whipple operation made it possible to re-establish continuity of the important gastrointestinal, hepatic, and pan-

creatic tracts after excision of important structures and regional tissue in the upper abdominal area. Similarly carcinomas of the mid esophagus and lower esophagus became resectable lesions when Garlock developed the technique of replacement of lower esophageal continuity by thoracic relocation of the stomach. It is clear, then, that successful radical surgery must employ reconstructive steps in replacement of the tissues or organs lost by surgical excision. The employment of this principle in the surgery of carcinoma of the oral cavity may require the prior preparation of a tubed pedicle of skin and fat. This is usually the case when oral carcinomas of low grade malignancy have invaded the cutaneous surface. In many instances suitable coverage of double-faced soft tissue may be obtained immediately through the use of a small rotation flap or, for larger lesions, a temporal flap. In others, a flap from a distance must be employed because of topographic details. In cases in which information revealed by history and biopsy indicates that the carcinoma is of relatively low grade malignancy and is of slow growth, it is justifiable to delay the radical excision 2 weeks or so to prepare a pedicle or flap over the acromiopectoral region. The availability of such a flap changes the whole approach of the surgeon to the excisional procedure. There need be no hesitancy in the wide excision of skin, subcutaneous tissue, muscles, bone, and mucous membranes adjacent to the lesion, and the cure of the carcinoma unquestionably depends upon the generosity of the surgeon's sacrifice of such tissues. Moreover, when such a soft tissue flap or pedicle has been readied in advance, immediate bone grafting in substitution for malar or mandibular defects may be employed.

The rapidly growing and highly malignant carcinoma is one which is not suited to this plan, but the experienced clinician knows that the slowly growing carcinomas of the oral cavity make up the majority of such cases, many of which are denied the greatest benefits of radical surgery or are left in the misery of unacceptable facial deformity or such unendurable complications as salivary fistula. A plea is made for consideration, in advance of excisional surgery, of the techniques of reconstructive surgery in the management of carcinoma of the oral cavity with the goal of improved follow-up results.

THE RIGHT-SIDED APPROACH TO CANCER OF THE ESOPHAGUS

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IN THE FACE OF A NOTICEABLE TENDENCY at present toward pessimism regarding the cure of cancer of the esophagus, surgeons should attempt to improve their mode of attack upon this disease. This objective might be accomplished by more radical resection. Since the esophagus is in actual contact with such vital structures as the heart, aorta, and lung root, it is not to be expected that wide removal of the growth, including its surroundings, en bloc, according to the best principles of cancer surgery, will soon be practicable. There are two spheres, however, in which excision can be extended, namely, in increased length of esophagus above the growth and in the lymphatic drainage of the tumor.

The lymph glands in question are those which, in addition to the local posterior mediastinal group behind the pericardium and in contact with the aorta and the esophagus, lie below the liver about the celiac axis artery and its branches and in the gastrohepatic omentum. These glands are often involved in tumors of the middle and lower thirds of the esophagus, which comprise the majority of cancers of the organ. In cancer of the upper third of the esophagus the paratracheal and paraesophageal as well as the cervical groups may become involved. The lymph glands most likely to be missed are the subhepatic group, largely because of their inaccessibility. The importance of removal of these glands has been recently emphasized by Adams in an editorial aimed at countering the prevailing negativism toward this disease. Persisting cancer in these glands was the cause of death in 1 of the author's patients 2 years after resection of a cancer of the middle third of the esophagus and supra-aortic esophagogastrostomy.

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It is now widely admitted that the best exposure for radical removal of the thoracic esophagus is secured through the right chest, and considerable success has been reported with the laparotomy-thoracotomy technique first advocated by Lewis.

In approach from the left side to a tumor of the thoracic esophagus placed anywhere above the lower one-fifth, the aorta, and particularly the combination of the aortic arch and the lung root, makes dissection difficult, is apt to interfere with removal of the local lymph glands, tends to restrict the length of esophagus removed above the growth, makes dangerous damage to the azygos vein a distinct possibility in tumors at this level, and probably makes damage to the contralateral lung or its root more possible. Even after mobilization of the aorta, some of these objections remain.

General acceptance of the Lewis procedure has been retarded for several reasons. Among these has been the need for an abdominal and thoracic incision together with the inconvenience and possible danger of turning the patient from the supine to the lateral position in the middle of the operation. Another difficulty has been the usual one encountered when attempting total gastrectomy through an abdominal incision, namely, the inaccessibility for ligation of the high vasa brevia from the spleen to the cardia. Perhaps one of the most important objections to the Lewis technique, as well as to the commonly used left thoracotomy transdiaphrag-

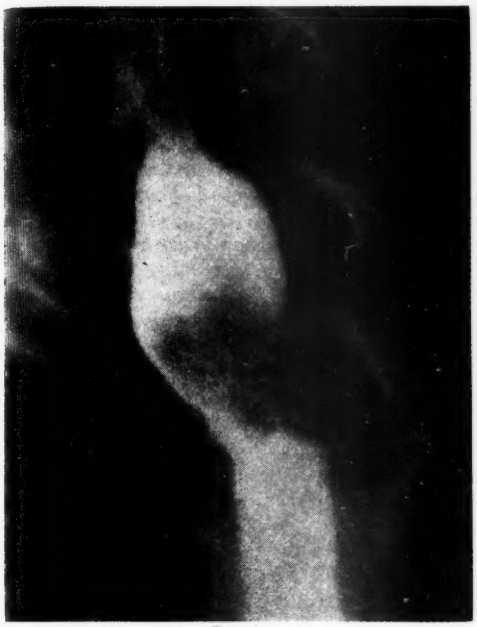

FIG. 1.

FIG. 2.

FIG. 1. Case 1. Roentgenogram of carcinoma of esophagus at, or just above, the thoracic inlet.
FIG. 2. Case 2. Roentgenogram of esophagogastrostomy high in the right chest after resection of carcinoma of midthoracic esophagus by a right thoracoabdominal approach.

matic approach, is the inadequate exposure of the subhepatic lymph glands.

It seems strange that more attention has not been given to the thoracoabdominal approach. The purpose of the present article is to advocate greater use of a right thoracoabdominal incision combined with a simple turning of the thorax made possible by the rotational capacity of the lower dorsal and lumbar spine. Such a maneuver gives good access to the whole length of the thoracic esophagus and stomach and, because of the turning of the liver upward into the chest made possible by the incision of the diaphragm, gives excellent exposure of the important lymph glands beneath the liver.

The only disadvantage of this approach, as compared with that of Lewis, appears to be the incision and resulting paresis of the diaphragm. Incision of the diaphragm is, however, an accepted part of the commonly used left thoracic approach to the lower third of the esophagus and is probably a small price to pay for improved exposure and more radical removal of the cancer. It is admitted, nevertheless, that in elderly patients with chronic bronchitis and emphysema paralysis of a hemidiaphragm may be a serious handicap in the postoperative period. It may have been enough to tip the scales adversely in 1 of the cases mentioned in this report. Because of the high location of the tumor in this case, however, requiring a pharyngogastrostomy for reconstruction, a right-sided anterior position of the stomach seemed the only practicable solution, as will be pointed out.

This procedure seems to overcome many of the objections to the Lewis approach, and most surgeons will agree that in the surgical attack on any cancer there are obvious advantages in going directly to the tumor at first and, after carefully examining it, planning one's course of action from there. For example, in some cases of esophageal tumor, it may be difficult or impossible to say, from x-ray or endoscopic evidence, whether the growth is cancer or a benign leiomyoma. In treating a leiomyoma, local shelling out of the tumor may be all that is required, and stomach mobilization in that case would be a costly redundancy.

An advantage of the right thoracoabdominal approach not often mentioned, and one which may also apply though probably with less ease to the Lewis procedure, is the choice which it presents to the surgeon of bringing up the stomach anterior to the liver and the right lung and in that way gaining a few more inches of stomach length than could be achieved when the organ is brought up posteriorly through the hiatus. This may be quite important in resections of tumors in the upper one-third of the esophagus.

The right thoracoabdominal approach lends itself well to the use of a jejunal Roux-en-y limb for esophageal reconstruction, should the surgeon elect to use this technique. Trial of this procedure in a few cases suggests that it is more time-consuming than is the use of the stomach for reconstruction, an important point in such a lengthy operation in the aged. The author has not as yet had an opportunity to testify to Allison's claim of a better functional result for jejunal, as opposed to stomach, reconstruction although he has noticed troublesome esophagitis with jejunal loop reconstruction, both with and without enteroenterostomy, after total gastrectomy. Perhaps the best use of the jejunal limb is in by-passing procedures in which the malignant or stenosed esophagus is left in situ, as in the procedures of Yudin or Robertson.

The technique advocated is based upon the fact that, with the pelvis fixed in the supine position, it is possible to rotate the chest almost 90 degrees into the lateral position.

The patient is placed supine on the table with the right buttock elevated about 4 inches on a sandbag. The pelvis is fixed to the table in this position with a wide adhesive band. The chest is then rotated into the lateral position by pulling the right shoulder forward and to the left, with a wide band of adhesive attached to the back of the right shoulder (spine of scapula). This band is then fixed, at a convenient point, to the table by the anesthetist. The right chest is opened through the bed of the resected seventh rib. The tumor is examined and if a radical resection is decided upon the esophagus is mobilized for as much length as required, by going at least 3 inches above the tumor and down to the hiatus in the diaphragm. Every effort is made to remove the local mediastinal lymph glands en bloc with the mass.

The thoracic incision is then temporarily covered with a towel, the fixing shoulder band is detached from the table, and the chest is allowed to rotate back into the supine position. The thoracic incision is next prolonged through the costal arch, across the right rectus abdominis muscle, to the midline above the umbilicus. The right diaphragm is divided from the front almost to the back of the chest, care being taken not to injure the inferior vena cava. The avascular left lateral ligament of the liver is divided, the left lobe of the liver is turned to the right, and the whole organ is rotated upward into the right chest, where it is held by an assistant. The abdominal inch or so of the esophagus and the whole length of the stomach are now laid bare. Both curvatures of the stomach are mobilized starting about 1 inch proximal to the pylorus and preserving the right gastric and epiploic vessels. The high vasa brevia from the spleen to the cardia still may be somewhat hard to get at, but, by careful traction on the stomach combined if necessary with a 20 to 30 degree tilt of the table to the right, they can be divided piecemeal between ligatures without risking the use of clamps which may cause tearing of the mesentery or the spleen.

The esophageal hiatus can be explored from above and below, and the stomach can be carefully eased up into the chest by slight traction on the esophagus from above and by gently pushing the stomach up from below. If it is found that the stomach will not reach high enough, the esophagus can be divided near the cardia, the cardiac orifice of the stomach closed, and the stomach brought up in front of the liver and lung. Mobilization of the duodenum will give still further length if required.

The chest is next rotated once more into the lateral position and the esophagogastrostomy anastomosis is done. If the anastomosis is being performed in the neck, the thoracic and abdominal incisions are closed, and the chest is allowed to rotate back into the supine position. Through an incision along the anterior border of the right sternomastoid prolonged downward, the medial one-third of the right clavicle and the anterior 2 inches or so of the first rib and costal cartilage are removed. The cervical esophagus is dissected, the chest is re-entered, and the anastomosis is completed.

Two cases illustrating the use of the approach advocated are briefly described.

In Case 1, with a carcinoma at such a difficult location as the thoracic inlet, anastomosis of the

stomach to the pharynx was necessary. In order to achieve this, it was necessary to bring the stomach along the shortest route from the pylorus to the cricoid cartilage, namely through the right chest in front of the liver and the right lung. Even in this position the stomach only barely reached the desired level, and while resection might not have been unduly difficult through a left thoracic approach reconstruction would have been impossible.

In Case 2 the proximity of the tumor to the root of the right lung might have exposed this structure to damage if the dissection had been undertaken from the left side.

CASE REPORTS

CASE 1. A. J., a 74 year old man, was admitted to the hospital in August 1951 with x-ray symptoms and endoscopic signs of a typical carcinoma of the esophagus just above the thoracic inlet. Roentgenogram of the chest showed, in addition, signs of an old pleurisy with obliteration of the costophrenic angle on the left side. Respiratory function tests showed emphysema but seemed to indicate sufficient reserve to undergo an extensive esophagectomy.

He was, therefore, explored by the technique described. A total esophagectomy was done and a pharyngogastrostomy was completed in the neck. The stomach was brought up anterior to the liver and the left lung, and it was clear at the time of the anastomosis that if the stomach had been brought up through the hiatus it would not have reached to the desired height. Apart from the extent of the surgery in a patient of this kind, no difficulties were encountered.

A productive cough proved very troublesome in the early days postoperatively, and despite repeated intratracheal suction and what seemed like encouraging recovery he died suddenly 4 days after operation.

Autopsy showed a rather large hemothorax on the right with atelectasis of the right lung. Considerable oozing had been encountered at the time of the dissection of the esophagus and due to our desire to shorten the time of the operation hemostasis had not been adequate. The partially disabled left lung combined with the atelectasis on the right had probably been responsible for the fatal outcome. The anastomosis was satisfactory at autopsy. It would seem that the combination of chronic bronchitis and emphysema, with the postoperative hemothorax (which catheter drainage did not cope with) causing compression of the right lung, had proved unsurmountable. Paresis of the right diaphragm may have contributed.

CASE 2. J. C., a 46 year old woman, was operated upon on February 28, 1955 by the right thoracoabdominal approach for a carcinoma of the midesophagus at and below the level of the azygos vein. The stomach in this case was brought up through the hiatus and an esophagogastrostomy high in the right chest was done with relative ease.

The postoperative course was satisfactory, she left the hospital on the fifteenth postoperative day swallowing well.

SUMMARY

In order to ensure more radical resection, the use of a right thoracoabdominal approach for the surgical treatment of carcinoma of all portions of the esophagus, except the first and last 1 or 2 inches, is advocated. The approach is made possible by rotation of the patient's thorax with the pelvis fixed to the operating table with a wide adhesive band.

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The Book Shelf

THE EXORCISM OF A SURGICAL LITERARY GHOST

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IN EXPLORING THE TRAILS leading backward into the origins of modern procedures, one is distracted by the apparition of references which on investigation have no substance. Founded on misconception and compounded by repetition of errors, they finally develop the appearance of fact. The exposure of these wraiths may clear the path for subsequent literary travelers. One such apparition has been found in the history of carotid ligation. It may be interesting to others to know the details of the detection of this "ghost."

Students of the early history of carotid ligation are led to a reference to Ernst Benjamin Gottlieb Hebenstreit, a Leipzig surgeon who lived from 1758 to 1803. At that time the Germans were considerably impressed by the works of Benjamin Bell (1) of Edinburgh, whose *A System of Surgery* had gone through many English editions, and finally came out in a German version in 1784 to 1790. The first two volumes of this German edition were by a translator who chose to remain anonymous; the last three were translated by Hebenstreit.

Bell had been greatly impressed by the work of the German surgeons, particularly by that of Heister, whose *System der Wundartzneykunst* had first appeared in 1739. Bell praised this work as being practically perfect in its day, and as containing everything discovered in previous ages and found useful in the surgical art. It was the first, he said, and still remained the only system of surgery worthy of the name. It was Bell's fairly obvious intention to become Heister's successor, the second in the line of great surgical systematizers. The anonymous translator of Bell's work, however, in a footnote on page 2 of the first volume of the German edition, set him deftly in his place. Heister, he remarked, deserves all the praise that Bell gave him, and the greatest present need of the art is to have a new and modern exposition constructed on Heister's plan. However, *only a German or Dutch physician is probably in a position to write such a work*, since other nations lack the necessary literary knowledge and skill. May the great Richter, he added, be pleased to accomplish this task! At the same time the translator evidently believed that, for a non-German, Bell had done extremely well, and he practically stopped the presses to add to his preface a brief last minute note, pointing out that Herr Hofrath Richter himself, in a volume just published, had spoken of Bell with high praise. With such an attitude toward his author, approving yet patronizing, it is not surprising that the translator felt free to introduce into Bell's text a considerable number of additions and observations, based largely on the works of contemporary German surgeons. When he took over the task of translation, Hebenstreit continued this practice. He originally meant to introduce the new matter in footnotes at appropriate places in the text, but this proved difficult and he added it as a large appendix (13) (pages 205 to 635) at the end of Volume 5.

For a long time there was a tradition that somewhere in these additions to Bell's text, Hebenstreit had inserted a description of an operation in which one of the carotid arteries was accidentally cut, but was promptly ligated by the surgeon, who thus kept the patient from bleeding to death. Several points of the story, as it was handed down from writer to writer, became a little vague. It was not always clear whether this was Hebenstreit's own experience, or that of another surgeon being reported. At any rate, it came to be known as "the Hebenstreit case." There was some uncertainty as to whether the operation was performed on the common carotid or on the external (facial) branch. The date was left extremely uncertain. The first author we have found to ascribe it to a certain year, 1786, was Günther, writing in 1864. The next precise date was 1929, when Cutter, apparently losing his way in the mazes of the Hebenstreit-Bell bibliography, decided that the case was first reported in print in 1793. He did not conjecture the date of the actual operation.

Working backward from book to book along several lines of citation, we finally came to Wishart's English translation of Scarpa, published in 1808. Here, in a note duly designated as coming from Wishart himself, is apparently the earliest outside reference to the case. He remarked: "Hebenstreit, in the 5th volume of his translation of Mr. B. Bell's System of Surgery, mentions a case which he met with, where the external carotid artery was wounded in the extirpation of a scirrhous tumour. The profuse hemorrhage, which instantly ensued, would soon have destroyed the patient, if the surgeon had not immediately recollected himself, and tied the trunk of the artery. The operation was successful, and the patient lived many years after it."

This casual reference to "the 5th volume," with no indication of date, page number, or edition, proved difficult to track down. The German translation of Bell went through three editions, published in 1784 to 1790, 1791 to 1798, and 1804 to 1810, respectively. Only the third edition was available at the Armed Forces Medical Library; it has a generous index, but this did not lead us to the desired passage. Later we located the second edition at the Bibliothèque Nationale in Paris, and still later, found all three in the John Crerar Library in Chicago. The first edition, especially, must be extremely rare.

Now that all the evidence is in, it is clear that the edition used by Wishart was the second. The relative dates exclude the third; his note citing "the 5th volume" which appeared in 1808, and the fifth volume of the third edition did not appear until 1809. Moreover, the wording of his statement makes it unlikely that he had used the first edition. Comparison of Hebenstreit's text in all editions showed the first to differ from the other two only in the closing sentence. In the first edition, the report of the case concludes: "The patient is still living many years after the operation." The second and the third say rather, "The patient lived many years after the operation." Apparently the patient had died before the writing of the second edition. Wishart's English summary of the case reflects the revised text; it ends with the words, "The operation was successful, and the patient lived many years after it." There can be little doubt that Wishart used Volume 5 of the second edition, published in 1798.

So far as we could find, Wishart's note is the sole source of information on this case for more than half a century. In that time, Samuel Cooper is the only student of the matter who seems to have consulted the Hebenstreit volumes, and he made matters worse, rather than better. Several other writers mentioned the case, however. In 1815, Hodgson quoted Wishart's note verbatim, but added nothing. According to the later survey by Pilz, there were two discussions of the general subject in 1833, by Zimmermann and by Walther, but we have been unable to find them in the literature. In 1845, Chevers examined all the records of carotid ligation that he could locate, and selected for discussion 14 cases in which undesirable after-effects on brain function had ensued. Emphasizing the perils of the operation, Chevers did not mention Hebenstreit's case. In 1847, South, an American, published an English translation of the German work of Chelius, adding a page of his own concerning the early history of carotid ligation. For the first recorded case, he quoted Wishart's note about Hebenstreit's fifth volume. There is now new information here. According to Pilz, there was a discussion in 1852 by Idzikowski which we have not found.

In 1857 another American, Wood, issued a well systematized survey of the history of carotid ligation, making fine distinctions as to the priority of special types. As the first dated case, he

accepted the operation on an attempted suicide by an English naval surgeon, Fleming, on October 9, 1803. He listed the first case in which the common carotid artery was tied in the extirpation of a tumor (Cogswell, November 4, 1803), the first case for aneurysm (A. Cooper, November 1, 1805), the first successful case for aneurysm (A. Cooper, June 22, 1808), and the first case for aneurysm-by-anastomosis (Travers, May 23, 1809). He also determined the first and second cases performed in the United States (November 4, 1803 and October 18, 1807), and the first and second performed in New York City (January 9, 1813 and November 28, 1816). He then reported 9 cases of his own and added brief reports on about 80 others. Wood introduced his survey with four reports he considered insufficiently authenticated. The first was that mentioned by "Hebenstreit in a German translation of *Bell's Surgery*." He gave no date, volume number, page, nor number of edition; it seems unlikely that he ever saw the Hebenstreit report.

In 1860 Ehrmann published in French an extensive discussion of 281 carotid operations, from which he tried to evaluate statistically the usefulness of ligating the artery. Fleming's (1803) is his first dated case. He mentioned "Hebenstreit, guer. (i.e., cured) Hodgson, *trad.* Breschet, t. II, p. 23," but starred the case as 1 of 10 for which historical details are entirely lacking. His authority is the French translation of the work of Hodgson, who, as we have seen, merely quoted Wishart. There is no indication that Ehrmann had seen Wishart's English, much less Hebenstreit's German translation.

Samuel Cooper deserves a special place in this account. In two of his works he mentioned the Hebenstreit case, apparently both times merely condensing Wishart's note. His *A Dictionary of Practical Surgery* contains an article on "Aneurism," and under the subhead "Carotid Aneurisms," he remarked, "The possibility of tying the carotid artery, in cases of wounds and aneurisms, without any injurious effect on the functions of the brain, now seems completely proved. . . . Hebenstreit, vol. 5, of his Translation of B. Bell's Surgery, mentions a case, in which the carotid artery was wounded, in extirpating a scirrhous tumour. The hemorrhage would have been fatal, had not the surgeon immediately tied the trunk of the vessel. The patient lived many years afterwards." *The First Lines of the Theory and the Practice of Surgery* appeared in 1807, but not until 1813, in the third edition, was a chapter on "Aneurisms" developed. In this chapter was stated: "Hebenstreit mentions a case, which he had met with, where the external carotid was wounded in the extirpation of a tumor; and the patient would quickly have fallen a victim to the hemorrhage, had not the surgeon instantly tied the trunk of the artery. The operation succeeded, and the patient lived many years afterwards." A footnote adds, "See his trans. of B. Bell's Surgery, Vol. 5."

Because of Cooper's importance at a later stage in this literary quest, it has seemed advisable to quote in full his early references to Hebenstreit. If these are compared with Wishart's note, and all three are compared with the German text given subsequently, it becomes reasonably clear that Wishart was translating from the original: "profuse hemorrhage" as "der ungeheure Blutsturz"; "immediately recalled himself" as "schnell sich gefasst." Cooper rewrote the Wishart account in briefer form and more natural English idiom. At this time Cooper apparently had not consulted Hebenstreit's German at all, but was merely paraphrasing Wishart, whose English edition of Scarpa was well known to him.

The vague reference to "Hebenstreit, vol. 5" was repeated in subsequent editions of Cooper's *Dictionary* down to 1822, when the article on Aneurism was rewritten. The reference was then changed to "Hebenstreit, vol. 4, p. 266, ed. 3," and the comment was added, "This is probably the earliest authenticated instance, in which ligature was applied to the carotid artery." The revised reference promptly appeared in Froriep's German translation of Cooper's *Dictionary*, and was retained in subsequent English editions to 1861. The reference in the *First Lines* was never changed; the old reference to "vol. 5" persisted in all editions to 1830, after which the Hebenstreit matter seems to have been left out entirely.

The only trouble with the revised reference is that it is entirely wrong. On page 266 of Volume 4 in Hebenstreit's third edition, the subject is goiter, together with aneurysms "seated directly on the course of one of the carotid arteries," to use Bell's own words. This is a point in the text at which a case of carotid ligation might well have been introduced, but it is not there. Two footnotes on the page, plainly labeled as observations of the translator, contain nothing on carotid ligation. It is difficult to imagine how

Cooper could have made this error, until one examines the sentence in which Hebenstreit leads up to the account of the operation. Here, to support his own recommendation as to these cases, he inserts a cross reference to another passage of Bell's, "See the fourth volume of this work, page 266." By some mischance this cross reference got into Cooper's *Dictionary* as if it were the proper reference to the passage describing the carotid ligation. It is a mistake, but also, it is clear evidence that Cooper or an assistant had actually consulted Hebenstreit's third edition.

We now find a man who in 1864 personally owned a copy of Hebenstreit's third edition, and who located the long-lost passage. Günther, in the fifth part of his massive and involved *Lehre von den blutigen Operationen*, noted that on page 332 of Volume 5 of the third edition he found what seemed to be the operation in question. He observed, however, that the account was plainly of an operation on the external carotid (arteria carotis facialis), not on the common carotid. He therefore, excluded the case from his long record of 259 instances of ligation of the common carotid and shifted it to his list of only 11 instances of ligation of the external carotid. He added that S. Cooper put the date of the operation in 1786. This is important if true, but we have been unable to verify it in any edition of Samuel Cooper's *Dictionary* or his *First Lines*.

The discovery, thanks to Günther, of the proper page reference in the third edition was welcome, but it did not solve all the problems. Hebenstreit himself prepared Volume 1 of the third edition for the press and wrote a preface for it, but died before it appeared. The work was carried on by a third translator, who like the first, chose anonymity. In these circumstances, could one feel sure that a passage in Volume 5 was by Hebenstreit? It might be by the third translator.

On examining copies of the first and second editions, the same report was found in both, with the slight variation noted previously, in the wording of the last sentence. In the first edition, the report was in the part of the work (Volumes 3 to 5) for which Hebenstreit is known to have been personally responsible. To Volume 5 of the first edition, he contributed a signed preface in which he discussed the sources of these additions to Bell's text, and his reasons for assembling them all at the end of the work. There can be no doubt that on page 217, the report of the carotid ligation is in Hebenstreit's own words. It was not his own case, and from the wording used ("Mir selbst ist ein Fall bekannt"), it is not clear whether he witnessed the operation. He evidently knew the surgeon and perhaps the patient well enough to keep track of developments over a considerable period of time. In the second edition, he noted the patient's intervening death and changed the last sentence of the report accordingly.

The original report in Volume 5 of the first edition appeared in 1790, when the patient was "still living many years after the operation." This leaves the date of the operation uncertain, although something might be surmised as to the possible limits. The operation could hardly have occurred earlier than 1778. Hebenstreit then was 20 years old, and it is unlikely that at an earlier age he would have been interested in surgical operations and their long-term results. On the other hand, the case could hardly have been later than 1786, four years before its first printed report. Could a surgeon, enthusiastically reporting on a remarkable case of another surgeon, speak of the patient having survived for "many years," when it had been only 4 years? He probably could; he would hardly call 3 years "many," but 4 he might. If such reasoning is correct, 1786 is about the latest plausible date for the operation.

This conclusion requires another critical look at Günther's second-hand remark concerning the date. On page 21 he stated definitely, "S. Cooper puts the year of this operation in 1786." On page 95, where he correctly entered the case as an operation on the external rather than the common carotid artery, he commented: "It is alleged (wird angegeben) that Hebenstreit, in a note to B. Bell's *System of Surgery*, remarks that in 1786 the arteria communis was ligated by a certain surgeon by reason of its having been accidentally cut (wegen einer Verletzung). In the copy belonging to me of the third edition of B. Bell (which Hebenstreit translated) in Volume 5, page 332 (1809), this case is introduced into the text in such a manner that it must be regarded as pertaining to the author himself." Whether "author" here means Bell or Hebenstreit is not quite clear—probably the former, which would be a completely wrong interpretation. On the other hand, the dating in 1786 is probably right, though one would like to dis-

cover such a statement somewhere in Cooper's writings.

The rest of the story is quickly told. In 1868 Pilz published in the *Archiv fur klinische Chirurgie* 6 elaborate tables describing 586 cases of carotid ligation, not including Hebenstreit. This deserves mention, since the next authority apparently thought Hebenstreit was included. In 1879 an American, Wyeth, published a table listing 789 ligations of the common carotid. Item 279 reads: "Hebenstreit. Arch. Klin. Chir. Removed tumor of parotid (wound of facial). Recovered." It is indicated that the patient was male, but no date for the operation was given. The casual reference to "Arch. Klin. Chir." can hardly refer to anyone but Pilz, who actually did not mention Hebenstreit at all.

For the next half century the case seems to have gone unnoticed. Then, in 1929, Cutter brought it up again and added to the confusion. Arguing that brain function may remain normal after ligation of one of the carotids, he referred to the case mentioned by Hebenstreit in his "Zusätze zu Benj. Bell's Abhandlung von den Geschwüren und deren Behandlung, 1793." As early as 1778 Bell had written a separate work entitled *A Treatise on the Theory and Management of Ulcers*, which Hebenstreit (14) immediately translated and published in German in 1779. In 1801, Bell incorporated *A Treatise on the Theory and Management of Ulcers* into the seventh edition of his *A System of Surgery*. Meanwhile, Hebenstreit in 1793 had supplemented his German edition with a 336 page volume of *Zusätze* (additions). This is the volume to which Cutter referred. In it there seems to be no trace of an operation on the carotid, nor would such a case be particularly expected in a work dealing with ulcers. Perhaps Cutter in his citation confused these *Zusätze* (published in 1793) to Bell's *Treatise* with the *Zusätze* (first published in 1790) to Bell's much larger *System of Surgery*. This is the apparent source of the evidently quite erroneous supposition that the carotid ligation was reported by Hebenstreit in 1793.

The latest comment to come to our attention is that of Dandy in 1937. He cited Cutter as having said that Herbenstreit (*sic*) reported the first carotid ligation in 1793, that Abernethy's first case was in 1798, and that Fleming's was in 1803. Dandy seems to have made no personal investigation of these cases.

Because of the rarity of the work, we append the German text and an English translation of Hebenstreit's report as printed in his first edition. In square brackets are indicated the changes made by Hebenstreit in his second edition, and those of his successor in the third. It should perhaps be pointed out that the word Hauptschlagader (main artery) at that period indicated one of the carotid arteries, while in modern German it means aorta. The report of the operation consists of about 8 lines, but to show it in its setting and to give some idea of Hebenstreit's professional astuteness, we quote the entire paragraph. Through all editions the passage is always in Volume 5, with page references as follows: first edition (1790), 217 to 218; second edition (1798), 240 to 242; third edition (1809), 332 to 334.

GERMAN TEXT

Es entsteht zuweilen eine Pulsadergeschwulst an einer oder beiden äussern Hauptschlagadern (Carotis). Man hat dieses Uebel nach heftigem Ausdehnen und Züruckbeugen des Halses, nach unmässigem Lachen und Husten beobachtet. [3rd edition begins: Aneurysmen an der äussern Carotis hat man nach heftigem Ausdehnen und Zurückbeugen des Halses, nach unmässigem Lachen und Husten entstehen sehn.] Lancisi widerrathet zwar in dergleichen Fällen die Operation [3rd edition: Lancisi widerrath in solchen Fällen die Operation]; da sie indessen doch [3rd edition omits doch] das einzige, wenn gleich ungewisse Rettungsmittel für den Patienten bleibt, dessen Tod sonst unvermeidlich ist, so glaube ich doch immer, dass man bey einem Aneurysma der Hauptschlagader auf einer Seite des Halses die Unterbindung wagen sollte, zumal da man dieselbe auch bey Verwundungen eben dieser Schlagader mit Nutzen angewendet hat. (Man sehe Bell, IV. Band, S. 94, 340.) [2nd edition: (Man sehe Bell, IV. Band, S. 95, 351.) 3rd edition, footnote: Siehe den vierten Band dieses Werkes, S. 266.] Mir sebst ist ein Fall bekannt, wo bey Ausrottung einer scirrhösen Geschwulst am Halse die äussern Hauptschlagader durchstochen wurde. Der ungeheure Blutsturz, welcher hier erfolgte hätte den Patienten in wenigen Minuten getödtet, wenn der Wundarzt nicht schnell sich gefasst, und das Gefäss unterbunden hätte. Der Erfolg war so glücklich, als man sich ihn wünschen konnte, und der Patient lebt noch jetzt viele Jahre nach der Operation [2nd and 3rd editions: und der Patient hat noch viele Jahre nach der Operation gelebt]. Ein weit grösseres Wagstück würde die Unterbindung wohl in dem Fall seyn, wenn sich an den äussern Hauptschlagadern auf beiden Seiten Aneurysmen befänden, und ich zweifle sehr, ob diese Operation hier jemals gelingen könnte. Denn ob gleich Swietens Versuch hiezu aufmuntern könnte, welcher einem Hunde beyde Haptschlagadern unterband, ohne dass das Thier im geringsten davon zu leiden schien [2nd and 3rd editions: ob gleich Valsalvas und Swietens Versuche hiezu aufmuntern könnten, welche Hunden beide Hauptschlagadern unterbanden, ohne dass diese Thiere in geringsten davon zu leiden schienen], (comment ad Boerh.

aphorism. 170, no. 3) so möchte sich doch hieraus keinesweges ein richtiger Schluss auf die Anwendbarkeit einer ähnlichen Operation bey Menschen machen lassen, weil bey diesen die Wirbelschlagadern in Ansehung ihres mehr gekrümmten Laufs, und der aufgerichteten Stellung des Körpers, den unterbrochnen Zufluss des Blutes durch die Hauptschlagadern wohl nicht so leicht als bey Hunden und andern vierfüssigen Thieren ersetzen können. [1st edition ends here; 2nd and 3rd add: Baillie beschreibt (Transact. of a Soc. for the improv. of med. and chir. Knowl., p. 121) die Leichenöffnung eines Mannes, dessen ganzes Arteriensystem eine Anlage zu widernatürlicher Erweiterung zeigte. Die rechte Hauptschlagader war dicht vor ihrer Theilung in die innere und äussere, doppelt so weit als gewöhnlich, und gänzlich mit fest geronnenem Blute angefüllt und verstopft. Die linke Hauptschlagader war an derselben Stelle zwar nicht ganz, aber doch grösstentheils verstopft. Baillie schliesst hieraus ebenfalls, dass man in Nothfall wohl beyde Hauptschlagadern unterbinden könne. Mir scheint es aber, dass man selbst aus dieser Beobachtung nicht so schliessen dürfe. Denn es ist doch wohl ein grosser Unterschied zwischen der Unterbindung, welche den Stamm des Gefässes auf einmal verschliesst, und jener Wirkung der Natur, welche eben so langsam, wie die Verstopfung der Stämme durch das geronnene Blut erfolgte, die anastomosirenden Seitenäste erweiterte.]

TRANSLATION

There occurs at times an arterial swelling on one or both of the outer main arteries (carotis). This difficulty has been observed after violent extension and retraction of the neck, or after immoderate laughing and coughing [3rd edition begins: Aneurysms in the outer carotis have been seen to occur after violent extension and retraction of the neck, or after immoderate laughing and coughing]. In such cases Lancisi advises against an operation; nevertheless, where this remains as the sole method, although an uncertain one, of saving the patient, whose death is otherwise inevitable, I myself believe that ligation ought always to be risked in case of aneurysm of the main artery on one side of the neck, especially if it has been necessary to use ligation because of the wounding of this same artery (see Bell, vol. 4, pp. 94, 340 [2nd edition: pp. 95, 351; 3rd edition in footnote: page 266]). A case has been known to me personally in which, during extirpation of a scirrhous tumor in the neck, the outer main artery was pierced. The tremendous hemorrhage which thereupon ensued would have killed the patient in a few minutes if the surgeon had not reacted quickly and ligated the blood vessel. The outcome was as fortunate as anyone could have wished, and the patient is still living many years after the operation [2nd and 3rd edition: and the patient lived many years after the operation]. Ligation in such a case would doubtless be a far greater risk if there were aneurysms present in the outer main arteries on both sides, and I gravely doubt if under those circumstances this operation could have succeeded. For though some encouragement for it could be derived from the experiment of Swieten, who ligated both of the main arteries in a dog without thereby causing the animal the slightest apparent suffering [2nd and 3rd editions: from the experiments of Valsalva and Swieten, who ligated both of the main arteries in dogs without thereby causing the animals the slightest apparent suffering] (see Commentary on Boerhave's Aphorisms, 170, no. 3), nevertheless it is quite inadmissible to draw from this a direct conclusion as to the usefulness of a similar operation on human beings, because in human beings it is probably not so easy as in dogs or other four-footed animals for the vertebral artery in view of its more circuitous course, and in view of the upright position of the human body, to compensate for the interrupted influx of blood through the main arteries [1st edition ends here; 2nd and 3rd add: Baillie describes (Transactions of a Society for the Improvement of Medicine and Chirurgical Knowledge, p. 121) the postmortem examination of a man whose entire system of arteries showed a condition of unnatural expansion. The right main artery, before its division into inner and outer, was thick—twice as much so as is customary—and was entirely filled up and blocked with solidly clotted blood. The left main artery, at that same point, was almost though not quite blocked. From this case Baillie draws the same conclusion (as Valsalva and Swieten), namely, that if necessary both of the main arteries can probably be ligated. It seems to me, however, that even on the basis of this observation such a conclusion is not warranted. For there certainly must be a great difference between the ligation, which shuts off the stem of the blood vessel abruptly, and that process of nature by which the stems are gradually blocked by the clotted blood while the anastomosed side branches are correspondingly dilated.]

From the evidence presented, it would seem that the name of Hebenstreit can be eliminated from the list of surgeons reputed to have been "first" to ligate the common or internal carotid arteries. May this "ghost" now rest in peace.

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Reviews of New Books

THE MONOGRAPH entitled *Die cervikalen Vertebral-Syndrome*[1] contains a symposium on the cervical vertebrae syndrome. It was written by several authors and represents the contemporary clinical views in Germany.

The subject, cervical vertebrae syndrome, is under study and there are differences of opinion, particularly as to the importance of etiologic factors and treatment. During the last decade more knowledge has accrued regarding the symptoms and organic changes of the lumbar spine. During the past five years the German literature has been concerned with the sympathetic nerve involvement and the nerve root involvement in the cervical spine. This is still quite a new field and there is still a great deal of confusion with regard to how much the symptoms are due to organic lesions and how much is functional.

The problem of disturbances of the cervical spine was reviewed at a meeting of the *Vereinigung Niederrheinisch-Westfalischer Chirurgen.* The clinical point of view was emphasized and the problem was discussed with consideration for the patient as a whole rather than as a local lesion of the cervical spine.

The first chapter of this volume is a discussion of the clinical-neurologic picture. The author describes neuralgia as a pain in the course of a nerve due to irritation of the nerve itself. Pain due to an inflammation of an organ will give a segmental type of pain distribution. In addition, in the cervical area there are disturbances due to an irritation of the sympathetic system. An irritation of the nerve will set up a protective reflex muscle spasm. This in itself will cause a certain type of muscular pain. Organic changes may occur in the cervical spine, including the normal arthritic changes which occur with age. Interference with the vascular supply in the cervical area has an effect on the nerves in that area. The author doubts the existence of a scalenus syndrome.

There is some relation between the sympathetic irritation in the cervical area and the occurence of pain in the shoulder. The shoulder may show a calcareous deposit by roentgenogram. Subluxations between the atlas and the axis cannot be overlooked entirely but they do not occur as frequently as the chiropractors believe. The operation for a medial displacement of the disc should be performed early. If the disc is laterally displaced, conservative treatment should be carried out.

Conservative treatment of the cervical syndrome is next discussed. The treatment by means of block of the sympathetic nervous system is emphasized. It is also important to carry out psychologic treatment. If the pain in the cervical region is due to a displaced disc there are symptoms in the upper extremity. In the case of the cervical syndrome due to inflammation, treatment with x-ray radiation is valuable. If there is inflammation in the cervical area infection might play a role or it may be due to a disturbance in mechanics. Psychogenic causes are important but these complicated factors must not overshadow the original idea of mechanical irritation as a causative factor. There is a relationship between precordial pain and pain in the neck. The connection is believed to be through the antonomic nerve system.

The origin of neurologic symptoms may be a cervical osteoarthritis. This may cause muscle tightness, root pain, and disturbances of the sympathetic system. There may be a narrowing of the foramen for the nerve due to hypertrophic changes. The fifth and sixth cervical vertebrae are most frequently involved. Pain in the head which simulates migraine may be the result.

In the sixth chapter a description of experiences with the cervical syndrome in a neurologic clinic are described. There the psychic factor is mentioned. In the seventh chapter the relationship between periarthritis of the shoulder area is described as a neurologic symptom secondary to disturbance in the cervical spine. Prognosis of the cervical vertebrae syndrome is discussed. Direct cord irritation sometimes occurs in the cervical area as the result of a disc prolapse.

The tenth chapter deals with the origin of neural symptoms in the cervical area due to mechanical causes. The final chapter discusses the value, if any, of osteopathic and chiropractic treatment in cases of cervical spine syndrome. Conservative methods of treatment are described. Local injection of novocain, head extension, hot packs, and massage are all utilized. Compared to the lumbar area need for surgical interference is infrequent. Orthopedic treatment consists in the correction of the posture and the use of extension. The need for electrocardiograms to differentiate the anginal symptoms was emphasized. Vitamin E, hormones, and the ketosteroids have all been used. One of the most useful treatments has been injection of novocain to the stellate ganglion.

This small volume contains thought-provoking material. The subject matter is of clinical interest because the condition occurs frequently and many of the answers are still unknown.

—*Emil D. W. Hauser.*

THE VOLUME entitled *Should the Patient Know the Truth*[2] is a well-intentioned collection of compositions. The thoughts and opinions of the participating writers, who are surgeons, physicians, nurses, lawyers, and clergymen representing the Protestant, Catholic, and Jewish faiths, are expressed in frank and well written essays. However, a few of the essays are too short, and 6 of the 23 articles were written by nurses reflecting, what appears to the reviewer, a somewhat magnified role of the nursing profession in this most difficult

[1]DIE CERVIKALEN VERTEBRAL-SYNDROME; EINE VORLAEUFIGE BILANG DER KLINIKER. Edited by F. Reischauer. 71 pages. DM 7.80. $1.85. Stuttgart: George Thieme Verlag, 1955.

[2]SHOULD THE PATIENT KNOW THE TRUTH; A RESPONSE OF PHYSICIANS, NURSES, CLERGYMEN, AND LAWYERS. Edited by Samuel Standard, M.D., and Helmuth Nathan, M.D. 160 pages. $3.00. New York: Springer Publishing Co., 1955.

modern medical problem. The expressed concepts vary from the forthright "unconditionally yes" by Owen H. Wangensteen to the belief (held by many of the other writers) that each problem should be strictly individualized. No hard and fast rules are in evidence in this volume.

All participating authors have displayed a great deal of courage, intelligence, and sincerity in formulating their opinions and conclusions. The representatives of religion offered decisive responses expressing the demands of religion and ethics. While this book does not offer a decisive answer to the problem "should the patient know the truth," the reader will nevertheless gain an insight and understanding of the ethics, morality, and philosophic responsibilities of the physician-patient relationship.

The format of this small volume with its imposing topic makes it an attractive and readable book. It undoubtedly will find a warm welcome because it fills a long overdue need. —*Robert Turell.*

AN EXCELLENT MONOGRAPH of 60 pages dealing with two subjects still presenting unsolved problems is entitled *Wiederherstellung des Harnweges und kuenstliche Harnableitung bei Erkrankungen des Harnleiters.*[3] In the reviewer's experience there is no satisfactory method of diverting the urine. Unfortunately, most of the writings upon the subject present a very rosy picture, and fail to call attention to the many pitfalls and the disastrous eventual outcome which so frequently follows a well executed, technical procedure. Boeminghaus approaches his subject in a realistic manner. He discusses the indications, the methods, the complications, and the possible success or failure of the various procedures. Although his treatment of the subject is far from complete and little is presented that is new, the author's frank approach to the subject is refreshing.

This monograph provides a pleasant evening of stimulating reading. It is well illustrated.

—*Frederick A. Lloyd.*

THE PREFACE TO THE VOLUME entitled *Kreislaufregulation; eine physiologische, pathophysiologische und klinische Studie*[4] is written by Prof. Dr. Ludwig Heilmeyer, one of the best known German hematologists and an excellent clinician. The volume contains 315 pages including 163 fine illustrations. After a very short introduction the authors discuss the vegetative nervous system and its relation to other organs, with special emphasis to the cardiovascular system. In very great detail the structure and function of this system is explained and illustrated by drawings. In the following chapter the physiology of the vegetative system and blood flow is considered. This is followed by a discussion of the principles of function of this system. In following paragraphs the reasons for false reaction in the vegetative system and their relation to the circulation and heart function are discussed. This is followed by a brief discussion of examination methods concerning such false reactions. The different forms of cardiovascular disturbances due to the vegetative nervous system are described in detail; shock, collapse, reflex reaction after myocardial infarction, cranial disturbances in the cardiovascular system are considered in turn. The next chapter discusses mostly the anxiety complex and its part in heart disease. This chapter is followed by an explanation of the psychic influence.

The last two chapters include a discussion of prognosis and therapy of cardiovascular disturbances which are due to false reaction in the vegetative nervous system.

The outline of the book is not too clear and the volume is not too easy to read. It is intended not only for clinicians but for physiologists and pathophysiologists as well. —*F. R. Lichtenheld.*

MANY PHYSICIANS familiar with the early editions of Joseph DeLee's classical work will have a feeling of nostalgia when they examine the recently published 11th edition of *Obstetrics*[5] by J. P. Greenhill. Comparison of this edition with the 10th, published in 1951, and with DeLee's first edition of 1913 graphically emphasizes the changes which obstetrics has undergone, not only during the past half century, but during the past few years as well. The author should be commended for his good judgment in retaining some excellent material from earlier editions which should not be lost to students.

Actually, this edition is greatly changed from previous ones. Illustrations and details in the text which are no longer pertinent have been sifted out. There are 125 new illustrations. The leisurely style and phraseology of earlier editions has been reworded into the shorter and more direct sentences of modern medical literature. The subject matter has been rearranged so that it is more useful to the student. Much vital information has been added. New chapters include ones on endocrine changes and diseases during pregnancy, the induction of labor, prolonged labor, roentgenology in obstetrics, fetal erythroblastosis and the Rh factor, analgesia and anesthesia, and diseases of the nervous system. The author has followed recent developments closely as is evidenced by the discussions of afibrinogenemia associated with obstetric hemorrhagic disorders, the association of retrolental fibroplasia with prolonged oxygen administration to premature infants, hyaline membrane disease, and the lower nephron syndrome. Moreover, the volume contains new data regarding a number of various other subjects.

The obstetrician and gynecologist will find things in Greenhill's *Obstetrics* with which he will disagree just as he will in most other textbooks. He will also find that it is up-to-date, authoritative, and clearly written. It is, as its predecessor was, a major textbook of value to all who are interested in obstetrics.

—*John W. Huffman.*

[3]WIEDERHERSTELLUNG DES HARNWEGES UND KUENSTLICHE HARNABLEITUNG BEI ERKRANKUNGEN DES HARNLEITERS. By Prof. Dr. H. Boeminghaus. 60 pages, 53 illustrations. DM 15. $3.60. Stuttgart: Georg Thieme Verlag, 1955.

[4]KREISLAUFREGULATION; EINE PHYSIOLOGISCHE, PATHOPHYSIOLOGISCHE UND KLINISCHE STUDIE. By H. Reindell, E. Schildge, H. Klepzig, and H. W. Kirchoff. With a foreword by Prof. Dr. Ludwig Heilmeyer. 315 pages, 69 illustrations. DM 39.60. $9.40. Stuttgart: Georg Thieme Verlag, 1955.

[5]OBSTETRICS. By J. P. Greenhill, M.D. 11th ed. 1088 pages, 1170 illustrations. Philadelphia and London: W. B. Saunders Co., 1955.

THE VOLUME entitled *Lehrbuch der praktischen Orthopaedie*[6] is a textbook of practical orthopedics. It represents the fundamental ideas taught by Spitzy and was written by five of his former students, all of whom are recognized authorities in the field of orthopedics. The material is arranged according to age periods. There is a section which describes special orthopedic techniques such as the use of plaster, special operations for bones and joints, and the description of an orthopedic examination.

The second section is concerned with orthopedics in children from 1 to 12 years of age.

The third division is devoted to adolescent orthopedics, patients from 12 to 20 years of age. The fourth section is concerned with adult orthopedics, and finally, there is a section on amputations and prostheses. Each part was written by the man who has had the most experience with that particular phase of orthopedics, but all of the authors have a common tie in that they follow the principles of their former professor.

The book is concerned with investigation and recognition, prophylaxis and treatment, and finally the cure of congenital and acquired deformities as well as disturbances in posture and kinetics. It is based primarily on material observed during the last 50 years. In earlier years orthopedics was concerned with congenital deformities—rickets, tuberculosis, and paralysis. Following the first World War there was an extraordinary number of war wounds and amputations. Prosthesis techniques were developed as the result of the tremendous number of accidents in industry and transportation as well as of war injuries. Disorders due to mechanical strain and tension have also increased and have more than balanced the decrease due to prevention of rickets. The cases resulting from the second World War did not differ greatly from those of the first World War but there was a much larger number. The suffering and lack of food as a result of the war had a serious effect on the orthopedic material. The increase in longevity has made the number of arthroses a more important orthopedic problem. The introduction of arthroplasty and surgery for ruptured intervertebral discs also influenced the trend of orthopedic surgery.

Tremendous advances in surgery for orthopedic conditions in the adult have been seen in England, America, Germany, and Austria. Advances in all the other branches of medicine have influenced modern orthopedics. These developments are described by the authors.

Under children's orthopedics the author discusses congenital clubfeet, torticollis, and scoliosis. In considering scoliosis he discusses the importance of the intervertebral disc as an etiologic factor. There is an excellent chapter on dysplasias of the hip with conservative and surgical treatment. Poliomyelitis, spastic paralysis, and tuberculosis receive a complete description. Under adolescent orthopedics epiphyseal disturbances and osteomyelitis are considered. A great deal of attention is given to degenerative arthritis in connection with adult scoliosis. In the treatment of the adult conditions the importance of giving relief is stressed even though a cure cannot be obtained.

The authors have managed to arrange the material so that it is practical and does not become redundant. The ample illustrations are fresh and distinct and add much to keep the interest in this large textbook.

This is a modern textbook representing a comprehensive view of German orthopedics. The book is a credit to the authors and to their very able and gifted professor, Dr. Spitzy. —*Emil D. W. Hauser.*

AN EXCELLENT REVIEW of diseases of the spine from the viewpoint of the radiologist is contained in *The Spine; a Radiological Text and Atlas.*[7] It is easy to read, and includes much interesting and instructive material.

The opening chapter is devoted to the embryologic development of the spine, functional architecture, and the radiologic examination of the normal spine. In this chapter, some x-ray technique is illustrated and described; however, throughout the book technique is not an important element and is only discussed when pertinent to special problems. Malformations of the spine, diseases of congenital, endocrine, or metabolic origin are discussed in the second and third chapters. The section on scoliosis included in this discussion is quite limited and is not complete enough to be of value to the orthopedist or to the practitioner concerned with correction of this particular spine deformity.

Other chapters in the book include diseases of inflammatory and degenerative nature, neoplasms, trauma, and the intervertebral disc. Still other chapters include diseases of the spinal cord of hematopoietic origin, collagen, and reticuloendothelial systems.

Throughout the book references to the discussion at hand are given. An excellent bibliography has been compiled. The discussion of each problem is not limited to x-ray interpretation, but includes pathology, anatomy, and some clinical data when necessary for clarification of the situation.

The illustrations on the whole are good. At first glance, it would seem that some reproductions of the roentgenograms are not particularly good; however, it will be noted that the particular pathology that is discussed is well illustrated while the remainder of the film may be over or under exposed. Pages devoted to larger illustrations might be of value in some cases.

The book will be useful to the student in radiology, to the orthopedist and neurologist, and, on occasion, to the pediatrician. —*William A. Larmon.*

AN EXTREMELY COMPREHENSIVE VOLUME entitled *The Skin*[8] by Arthur C. Allen is based on the clinicopathologic concept of correlation. There are 28 chapters adding up to over 1,000 pages. A most satisfactory index is present at the book's end, and an up-to-date bibliography is included at the end of each chapter. Here, however, the headings are broken

[6] LEHRBUCH DER PRAKTISCHEN ORTHOPAEDIE. By Doz. Dr. Walther Aberle, Prof. Dr. Philipp Erlacher, Dr. Alexander Hartwich, Dr. Alfons Königswieser, and Prof. Dr. Oskar Stracker. 549 pages, illustrated. $24.50. Wien-Bonn: Wilhelm Maudrich, 1955.

[7] THE SPINE; A RADIOLOGICAL TEXT AND ATLAS. By Bernard S. Epstein, M.D. 539 pages, 721 illustrations on 331 figures. $16.50. Philadelphia: Lea & Febiger, 1955.

[8] THE SKIN; A CLINICOPATHOLOGIC TREATISE. By Arthur C. Allen, M.D. 1048 pages, 495 full page illustrations. $25.00. St. Louis: The C. V. Mosby Co., 1954.

down in order to simplify reference to the separate entities. When contributory, very thorough classifications head each chapter. Terms and obscure entities are defined and clarified. Though the morphologic alterations are stressed (the author being primarily a pathologist), there is much valuable clinical data. Many excellent black and white photographs of the patients are presented along with photomacrographs and photomicrographs of the entities as specimens. These are delineated topographically and elaborated upon in the written part of the text.

There is a simple outline of the anatomy, embryology, and physiology. Confusing and similar terms are explained in a separate section.

Space is allotted in proportion to the importance of each entity. Not too much controversial material is included.

As might be expected, particular comment is directed toward neoplastic disease. This is covered most thoroughly. The interest of Dr. Allen in nevi and malignant melanoma is well known. His conclusions are rather readily accepted.

The pages assigned to mycoses, to radiation changes, and to deficiencies are also much appreciated by this reviewer. There is competent analysis of the collagen diseases. Actually all sections are complete, some just stand out above the others.

This volume is a reference book. As such, it is of much value to many physicians. One could not say that it is for the use of the few—rather that it should be available to those who diagnose and/or treat patients who are afflicted with diseases of the skin.

Binding and printing are in keeping with the excellence of the material. —*M. C. Wheelock.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

Cancer Cells. By E. V. Cowdry. 677 pages, 137 illustrations. $16.00. Philadelphia and London: W. B. Saunders Co., 1955.

Office Procedures. By Paul Williamson, M.D. 412 pages, illustrated. $12.50. Philadelphia and London: W. B. Saunders Co., 1955.

Sistema Nervioso Autonomo; Anatomía, Fisiología y Aplicaciones Quirúrgicas. By James C. White, Reginald H. Smithwick, and Fiorindo A. Simeone. First Spanish edition translated by Dr. Vicente F. Pataro. 542 pages, 108 illustrations. Buenos Aires: Editorial Artecnica, 1955.

Textbook of Endocrinology. Edited by Robert H. Williams, M.D. 2nd ed. 776 pages, 175 illustrations. $13.00. Philadelphia and London: W. B. Saunders Co., 1955.

The President's Review from the Rockefeller Foundation Annual Report 1954. 145 pages, illustrated. New York: The Rockefeller Foundation, 1955.

La Pression Interfragmentaire dans L'osteosynthèse. By Docteur Jean-Pierre Razemon. 123 page, illustrated. Lille: Imprimerie Morel et Corduant, 1955.

Zwanglose Abhandlungen auf dem Gebiete der Frauenheilkunde. Edited by Prof. Dr. Robert Schröder. Vol. 18. Das Parametrium; funktionelle Anatomie der Ligamentzuege sowie ihre Beziehung zur Zervix und Beckenwand besonders waehrend der Schwangerschaft und Geburt. By Wilhelm Langreder. 188 pages, 122 illustrations. DM 33.50 Leipzig: Veb Georg Thieme, 1955.

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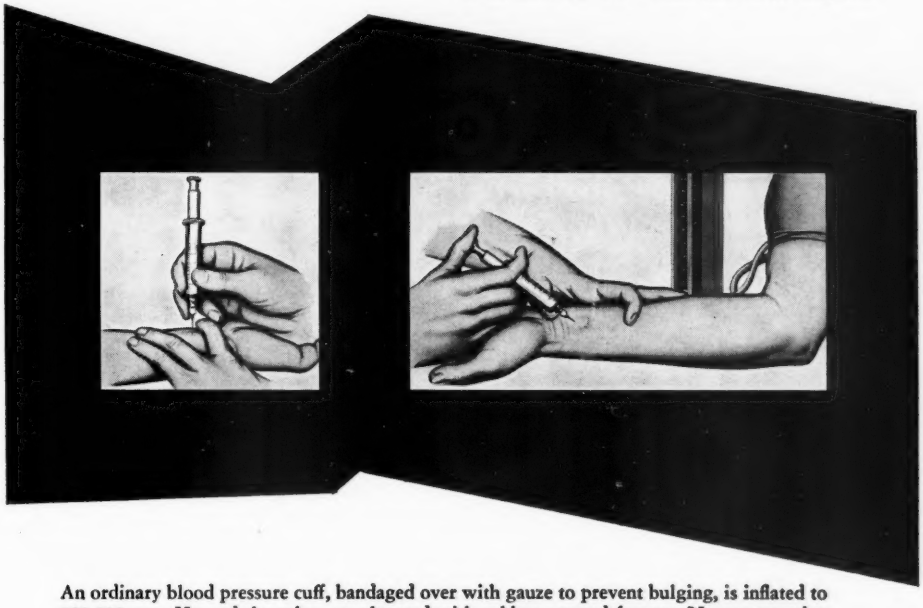

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1. Karp, M.; Lamb, V.E., and Benaron, H.B.W.: Am. J. Obst. & Gynec. 69:780 (April) 1955.

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